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(54) **ENDOTHELIN ANTAGONIST**
ENDOTHELIN-ANTAGONISTEN
ANTAGONISTE DE L'ENDOTHELINE

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Description

[0001] The present invention relates to a novel use of a prostanoid acid compound wherein the skeletal carbon atoms in α -chain are increased as endothelin antagonist.

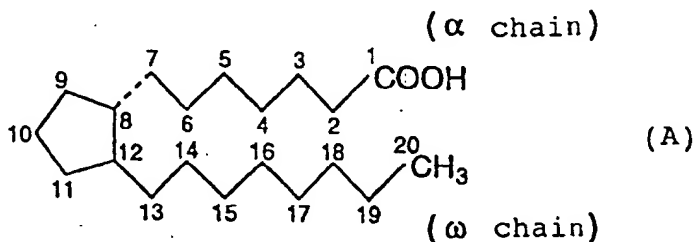
[0002] The antagonist according to the present invention is useful as a treating agent for a variety of diseases participated of endothelin.

BACKGROUND ART

[0003] Endothelin is an endogenous bioactive peptide composed of 21 amino acids, and three types of which, i.e., endothelin-1, endothelin-2, and endothelin-3 are known.

[0004] Endothelin is a bioactive substance for continuously constricting vascular or non-vascular smooth muscle in direct or indirect way (regulation of release of a variety of endogenous substances), and production of endothelin increases due to lesion of endothelium. Excessive production of endothelin is considered to be a cause for diseases such as hypertension, pulmonary hypertension, Buerger disease, primary Raynaud syndrome, asthma, eyegrounds (amphiblastrodes, chorioidea, and the like) diseases, diabetes, arterial sclerosis, renal failure, cardiac infarction, angina pectoris, cerebrovascular contraction, and cerebral infarction. Furthermore, it is known that endothelin is an important mediator with respect to multiple organ failures, and diseases such as disseminated intravascular coagulation due to endotoxin shock and the like as well as renal lesion induced by cyclosporin and the like. Moreover, it is also known that an endothelin concentration in blood increases after organ transplantation such as liver transplant.

[0005] Prostanoid acid is a skeletal compound constituting a common structural feature of natural prostaglandins (PG) groups and is represented by the following structural formula:



[0006] Natural PG groups are classified based on the structural feature of five-membered ring into PGA group, PGB group, PGC group, PGD group, PGE group, PGF group, PGG group, PGH group, PGI group, and PGJ group; and further they are classified as follows on the basis of presence or absence of unsaturation and oxidation at their chain portions:

numerical subscript 1 .. 13,14-unsaturated-15-OH
 numerical subscript 2 .. 5,6- and 13,14-di-unsaturated-15-OH
 numerical subscript 3 .. 5,6,13,14- and 17,18-tri-unsaturated-15-OH

[0007] Moreover, the PGF group is classified into α (hydroxy group is in alpha-configuration) and β (hydroxy group is in beta-configuration) based on the configuration of hydroxy group at 9-position. In addition, a compound having oxo group in place of hydroxy group at 15-position is also known.

[0008] With respect to action of prostanoid acid compound on endothelin, it has been reported, for example, that PGE_2 inhibits renal endothelin inducible vasoconstriction in rat, and that prostacyclin (PGI_2) moderates renal endothelin inducible vasoconstriction in dog.

[0009] However, any of these prostanoid acid compounds is the one wherein the basic carbon atoms in α -chain are 7, and hence, they do not correspond to the prostanoid acid compound wherein the skeletal carbon atoms in α -chain increase.

[0010] US Patent No. 3,974,195 and European Patent Application Laid-Open No. 0453127 (corresponding to Japanese Patent Kokai Hei 5-58992) describe a compound wherein the skeletal carbon atoms in α -chain are increased by 2, but there is no description as to the action with respect to endothelin in these both publications.

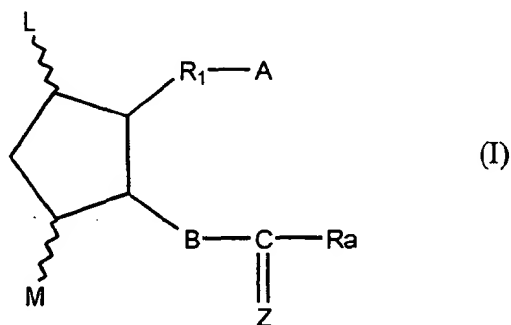
[0011] Other prostaglandin compounds are also described; for example U.S. patents No. 5,292,754 and 4,166,187 describe deoxy prostaglandin compounds, European patents No. 0435443 and 0503887 describe 15 keto prostaglandin compounds and French patent 2317915 describes lactol derivative of prostaglandin compounds. However, these

documents do not contain any description as to the action with respect to an endothelin.

DISCLOSURE OF THE INVENTION

[0012] An object of the present invention is to provide an endothelin antagonist useful for treating a variety of diseases and pathologies participated by endothelin.

[0013] According to a first aspect of the invention there is provided the use of a prostanoid acid compound represented by the general formula (I):

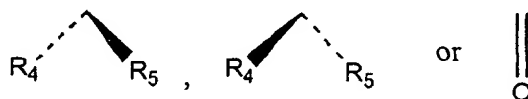


wherein L and M are hydrogen, hydroxy, halogen, C₁₋₆ alkyl, hydroxy(C₁₋₆) alkyl, or oxo wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is -CH₂OH, -COCH₂OH, -COOH or its functional derivatives;

B is -CH₂-CH₂-, -CH=CH-, -C≡C-, -CH₂-CH₂-CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -C≡C-CH₂-, or -CH₂-C≡C-;

Z is



wherein R₄ and R₅ are hydrogen, hydroxy, C₁₋₆ alkyl, or C₁₋₆ alkoxy wherein R₄ and R₅ are not hydroxy and C₁₋₆ alkoxy at the same time;

R₁ is a divalent saturated or unsaturated aliphatic hydrocarbon residue having 7 to 12 carbon atoms, which is unsubstituted or substituted by halogen, oxo, or aryl; and

R_a is a saturated or unsaturated C₁₋₁₄ aliphatic hydrocarbon residue which is unsubstituted or substituted by halogen, oxo, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkanoyloxy, cyclo(C₁₋₆)alkyl, aryl, or aryloxy for producing a pharmaceutical composition for the treatment of a disease caused by excess of endothelin.

[0014] The present inventor has eagerly studied with respect to biological activity of a prostanoid acid compound wherein the skeletal carbons in the α-chain are increased. As a result, it has been surprisingly found that a prostanoid acid compound of Formula (I) having at least 8 carbon atoms in the α-chain has extremely strong antagonistic action as compared with that of heretofore known prostanoid acid compounds having 7 carbon atoms in the α-chain, so that the present invention has been completed.

[0015] Nomenclature of the prostanoid acid compounds herein uses the numbering system of the prostanoid acid represented in the formula (A) shown above.

[0016] While formula (A) shows a basic skeleton having twenty carbon atoms, the carbon atoms in the present invention are not limited thereto. Namely, the numbers of the carbons constituting the basic skeleton are assigned in such that number 1 is assigned to carboxylic acid, numbers 2 to 7 are given to the carbons on the α-chain in accordance with the order directing to the five-membered ring, numbers 8 to 12 are assigned to the carbons of the five-membered

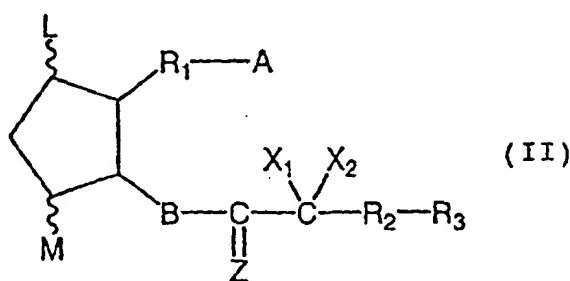
ring, and numbers 13 to 20 are given to the carbons on the ω -chain, respectively. However, in the case where carbon atoms decrease on the α -chain, numbers are successively deleted from the 2-position, while in the case where carbon atoms increase on the α -chain, nomenclature is made in such that the 2-position is substituted by any substituent in place of the carboxyl group (1-position). Likewise, in case of decreasing carbon atoms on the ω -chain, the number of carbon atoms is successively deleted from 20-position, while in case of increasing carbon atoms on the ω -chain, nomenclature is made in such that the carbon atoms at 21-and thereafter positions are considered to be substituents. Further, with respect to steric configuration, it is in accordance with that involved in the above indicated basic skeleton unless otherwise specified.

[0017] For instance, while PGD, PGE, and PGF mean compounds each containing hydroxy group(s) at 9-position and/or 11-position, the present invention includes also compounds containing any other group(s) in place of hydroxy group(s) at 9-position and/or 11-position. In case of nomenclature of these compounds, it is made in the form of 9-dehydroxy-9-substituted compound or 11-dehydroxy-11-substituted compound. In case of containing hydrogen in place of hydroxyl group, it is simply named as 9(11)-dehydroxy compound.

[0018] As mentioned above, while nomenclature of prostanoid acid compound is made on the basis of prostanoid acid skeleton in the present invention, when the above described compound has the same partial structure as that of prostaglandins, there is a case where an abbreviation of PG is also utilized for simplicity. In such case, a PG compound having two increased skeletal carbon atoms in α -chain, i.e., a PG compound having 9 skeletal carbon atoms in α -chain is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Likewise, a PG compound having 11 skeletal carbon atoms in α -chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound. Furthermore, a PG compound having two increased skeletal carbon atoms in ω -chain, i.e., a PG compound having 10 skeletal carbon atoms in ω -chain is named as 20-ethyl-PG compound. The naming may also be made based on IUPAC nomenclature. Examples of naming according to both the nomenclature are shown in the following Examples.

[0019] The prostanoid acid compounds used in the present invention are the ones wherein the skeletal carbon atoms in α -chain may be 8 or more, preferably 8 to 13, more preferably 9 to 13, and particularly preferably 9 to 11. Accordingly, any of the following compounds may be used, and they are, for example, PG₁ compounds having double bonds at 13-14 positions and a hydroxy group at 15-position, PG₂ compounds having further double bonds at 5-6 positions, PG₃ compounds having further double bonds at 17-18 positions, 15-keto-PG compounds having further an oxo group in place of hydroxy group at 15-position, 15-dehydroxy-PG compounds having hydrogen in place of hydroxy group at 15-position, or either 13,14-dihydro-PG compounds wherein these double bonds at 13-14 positions are single bonds, or 13,14-didehydro-PG compounds wherein the double bonds at 13-14 positions are triple bonds. Moreover, examples of substituted compounds and derivatives include compounds wherein the terminal carboxyl group in α -chain of the above described prostanoid acid compound containing 8 or more skeletal carbon atoms in α -chain has been esterified, the physiologically acceptable salts thereof, compounds wherein the carbon atoms in ω -chain are increased, compounds having side chains (e.g., 1 to 3 carbon atoms) on α - and ω -chains, compounds having substituent(s) such as hydroxy, halogen, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, and oxo, or double bond(s) on the five-membered ring, compounds having substituent(s) such as halogen, oxo, and aryl on α -chain, compounds having substituents such as halogen, oxo, hydroxy, lower C₁₋₆ alkoxy, C₁₋₆ alkanoyloxy, cyclo(C₁₋₆)alkyl, aryl, and aryloxy on ω -chain, and compounds having substituent such as C₁₋₆ alkoxy, C₁₋₆ alkanoyloxy, cyclo(C₁₋₆)alkyl, aryl, and aryloxy at the terminal of the ω -chain of which is shorter than that of normal prostanoid acid.

[0020] A preferred compound used in the present invention is represented by the formula (II):



wherein L and M are hydrogen, hydroxy, halogen, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, or oxo wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is -CH₂OH, -COCH₂OH, -COOH or its functional derivatives;

B is -CH₂-CH₂-, -CH=CH-, -C≡C-, -CH₂-CH₂-CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -C≡C-CH₂-, or -CH₂-C≡C-;

Z is



wherein R_4 and R_5 are hydrogen, hydroxy, C_{1-6} alkyl, or C_{1-6} alkoxy wherein R_4 and R_5 are not hydroxy and C_{1-6} alkoxy at the same time;

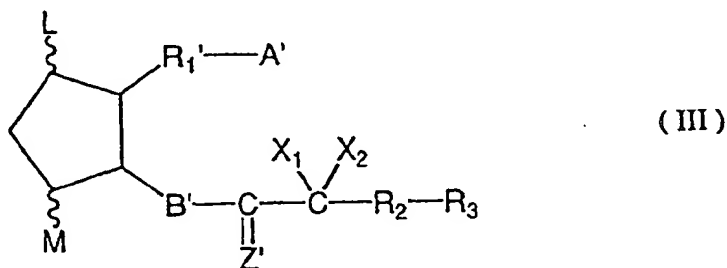
X_1 and X_2 are independently hydrogen, C_{1-6} alkyl, or halogen;

R_1 is a divalent saturated or unsaturated aliphatic hydrocarbon residue having 7 to 12 carbon atoms, which is unsubstituted or substituted by halogen, oxo, or aryl;

R_2 is a single bond or C_{1-6} alkylene; and

R_3 is C_{1-6} alkyl, C_{1-6} alkoxy, cyclo(C_{1-6})alkyl, aryl, or aryloxy.

[0021] Furthermore, the present invention relates to a compound represented by the general formula (III) :

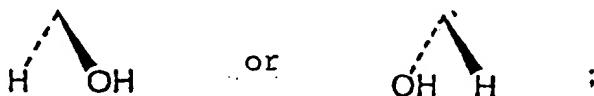


wherein L and M are hydrogen, hydroxy, halogen, C_{1-6} alkyl, hydroxy(C_{1-6})alkyl, or oxo wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A' is $-COOH$, or its functional derivatives;

B' is $-CH_2-CH_2-$;

Z' is



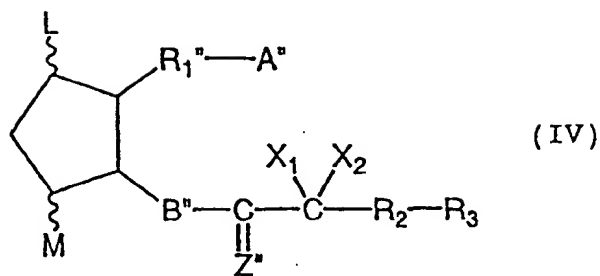
X_1 and X_2 are hydrogen, C_{1-6} alkyl, or halogen wherein at least one of X_1 and X_2 is a halogen;

R_1 is a divalent saturated or unsaturated aliphatic hydrocarbon residue having 8 carbon atoms, which is unsubstituted or substituted by halogen, oxo, or aryl;

R_2 is a single bond or C_{1-6} alkylene; and

R_3 is C_{1-6} alkyl, C_{1-6} alkoxy, cyclo(C_{1-6})alkyl, aryl, or aryloxy.

[0022] Moreover, the present invention relates to a compound represented by the general formula (IV):



wherein L and M are hydrogen, hydroxy, halogen, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, or oxo wherein M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

15 A'' is -COOH, or its functional derivatives;

B'' is -CH₂-CH₂-, or -CH=CH-;

Z'' is



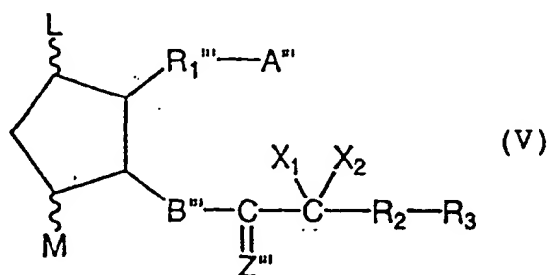
25 X₁ and X₂ are independently hydrogen, C₁₋₆ alkyl, or halogen;

R₁'' is a divalent saturated or unsaturated aliphatic hydrocarbon residue having 8 carbon atoms, which is unsubstituted or substituted by halogen, oxo, or aryl;

R₂ is a single bond or C₁₋₆ alkylene; and

R₃ is C₁₋₆ alkyl, C₁₋₆ alkoxy, cyclo(C₁₋₆)alkyl, aryl, or aryloxy.

30 [0023] Still further, the present invention relates to a compound represented by the general formula (V):



45 wherein L and M are hydrogen, hydroxy, halogen, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, or oxo wherein M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

50 A''' is -COOH, or its functional derivatives;

B''' is -CH₂-CH₂-, or -CH=CH-;

Z''' is



X₁ and X₂ are independently hydrogen, C₁₋₆ alkyl, or halogen;

R₁''' is a divalent saturated or unsaturated aliphatic hydrocarbon residue having 10 carbon atoms, which is unsubstituted or substituted by halogen, oxo, or aryl;

R₂ is a single bond or C₁₋₆ alkylene; and

R_3 is C_{1-6} alkyl, C_{1-6} alkoxy, cyclo(C_{1-6})alkyl, aryl, or aryloxy.

[0024] In the above described formula, the term "unsaturated" appeared in R_1 , R_1' , R_1'' , R_1''' , and R_a means to include at least one or more of double bond(s) and/or triple bond(s) isolatedly, separately, or serially present between carbon atoms of the straight or side chain.

[0025] The term " C_{1-14} aliphatic hydrocarbon" means a hydrocarbon having a straight chain of 1 to 14 carbon atoms which may have side chain (wherein the side chain has preferably 1 to 3 carbon atoms), and preferably, 1 to 9 carbon atoms.

[0026] The term "aliphatic hydrocarbon having 7 to 12 carbon atoms" means a hydrocarbon having a straight chain of 7 to 12 carbon atoms which may have side chain (wherein the side chain has preferably 1 to 3 carbon atoms). Preferable is such that the hydrocarbon has 8 to 12 carbon atoms, and particularly preferable is such that the hydrocarbon has 8 to 10 carbon atoms.

[0027] The term "halogen" includes fluorine, chlorine, bromine, and iodine.

[0028] The term " C_{1-6} " means a group having 1 to 6 carbon atoms unless otherwise specified.

[0029] The term " C_{1-6} alkyl" means a straight- or branched-chain saturated hydrocarbon group having 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl.

[0030] The term " C_{1-6} alkoxy" means a lower alkyl-O- wherein the lower alkyl is as described above.

[0031] The term "hydroxy(C_{1-6})alkyl" means an alkyl as described above, which is substituted by at least one hydroxy group, for example, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, and 1-methyl-1-hydroxyethyl.

[0032] The term " C_{1-6} alkanoyloxy" means a group represented by the formula $RCO-O-$ wherein $RCO-$ is an acyl formed by oxidation of a C_{1-6} alkyl as described above, for example, acetyl.

[0033] The term " C_{1-6} cycloalkyl group" means a group formed by cyclization of a C_{1-6} alkyl group containing 3 or more carbon atoms as described above, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0034] The term "aryl" includes aromatic hydrocarbon rings or heterocyclic groups (preferably monocyclic groups) which may be substituted, for example, phenyl, tolyl, xylyl, and thienyl. An example of the substituent in this case includes halogen, and halogen substituted C_{1-6} alkyl group (wherein halogen atom and C_{1-6} alkyl group are as described above).

[0035] The term "aryloxy" means a group represented by the formula $ArO-$ (wherein Ar is an aryl group as described above).

[0036] The term "functional derivatives" of the carboxy group represented by A includes salts (preferably pharmaceutically acceptable salts), esters, and amides.

[0037] Examples of suitable "pharmaceutically acceptable salts" include nontoxic salts which are commonly used, and they are salts with inorganic bases, for example, alkali metal salts (sodium salt, potassium salt and the like); alkaline earth salts (calcium salt, magnesium salt and the like); ammonium salts; salts with organic bases, for example, amine salts (such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethylmonoethanolamine salt, lysine salt, procaine salt, and caffeine salt); basic amino acid salts (such as arginine salt, and lysine salt); tetraalkyl ammonium salts and the like. These salts may be manufactured from, for example, corresponding acids and bases in accordance with a conventional manner or salt exchange.

[0038] The esters includes aliphatic esters, for example, C_{1-6} alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, and 1-cyclopropylethyl ester; C_{1-6} alkenyl esters such as vinyl ester, and allyl ester; C_{1-6} alkynyl esters such as ethynyl ester, and propynyl ester; hydroxy(C_{1-6}) alkyl esters such as hydroxyethyl ester; and C_{1-6} alkoxy(C_{1-6})alkyl esters such as methoxymethyl ester, and 1-methoxyethyl ester as well as, for example, optionally substituted aryl esters such as phenyl ester, tosyl ester, t-butylphenyl ester, salicyl ester, 3,4-dimethoxyphenyl ester, and benzamidephenyl ester; and aryl(C_{1-6})alkyl esters such as benzyl ester, trityl ester, and benzhydryl ester. An example of amides includes mono- or di- C_{1-6} alkyl amides such as methylamide, ethylamide, and dimethylamide; aryl amides such as anilide, and toluidide; and alkyl or aryl sulfonyl amides such as methylsulfonyl amide, ethylsulfonyl amide, and tolylsulfonyl amide.

[0039] A preferred example of A -group includes $-COOH$, $-COOCH_3$,

$-COOCH_2CH_3$, $-COOCH(CH_3)_2$, and $-CONHSO_2CH_3$.

[0040] In the above described formula (I), configurations of the ring, α - and/or ω -chain(s) may be the same with or different from those of natural prostaglandins group. However, it is to be noted that the present invention includes also the mixtures of compounds having natural and nonnatural configurations.

[0041] An example of the typical compounds according to the present invention includes 2-decarboxy-2-(carboxy C_{1-6} alkyl)-PG compounds, particularly 2-decarboxy-2-(2-carboxyethyl)-PG compound, 2-decarboxy-2-(4-carboxybutyl)-PG compound, 5-fluoro-form, 6-keto-form, 11-dehydroxy-form, 16-fluoro-form, 16-methyl-form, 17-fluoro-form, 17-methyl-form, 18-methyl-form, 19-methyl-form, 20-methyl-form, 20-ethyl-form, 20-propyl-form, 18,19,20-trinor-17-phenyl-form and the like.

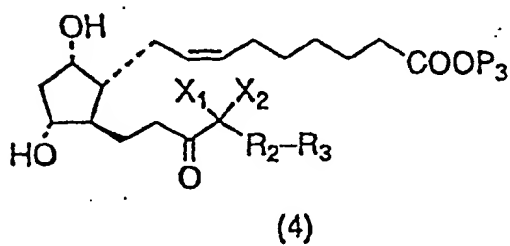
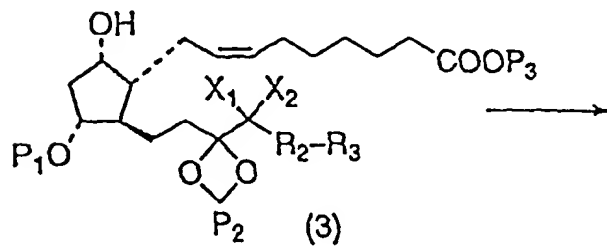
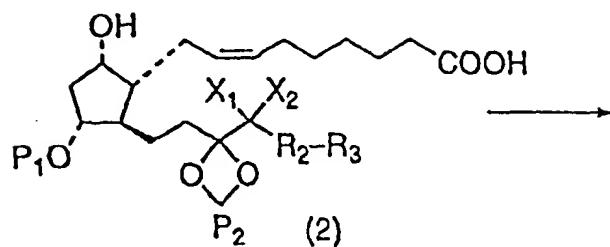
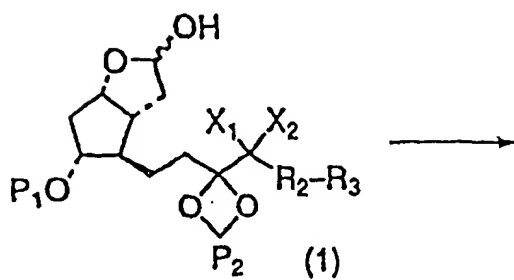
[0042] In the PG compounds used in the present invention, when 13-,14-positions are saturated and 15-position is oxo (i.e., in case of 13,14-dihydro-15-keto-form), there is a case where keto-hemiacetal equilibrium occurs as a result of formation of hemiacetal between the hydroxy at 11-position and the keto at 15-position.

[0043] In the case when such tautomers exist, a ratio of existence of both the tautomers are depend upon the structure of the other party or the types of substituents, and according to circumstances, either of tautomers exists predominantly. However, the present invention includes these both tautomers, and there is a case where a compound is indicated in accordance with either keto-form structural formula or nomenclature irrespective of presence or absence of such tautomers. In other words, this is only a manner for conveniences' sake, and there is no intention of excluding hemiacetal-form compounds.

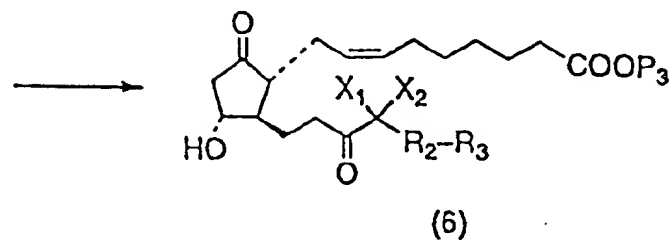
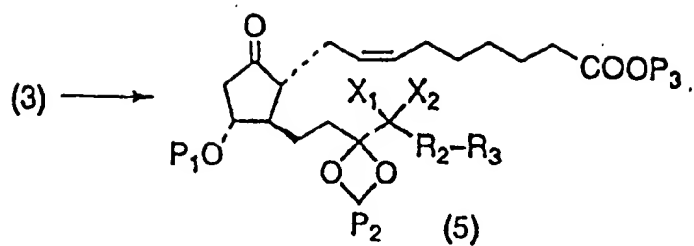
[0044] In the present invention, any of the individual tautomers, the mixture thereof, or optical isomers, the mixtures thereof, racemic modifications, and other isomers such as stereoisomers may be used for the same purpose.

[0045] While the compounds according to the present invention can be manufactured by a variety of methods, they may also be manufactured, for example, in accordance with the following Synthetic Chart. In the following Synthetic Chart, P₁, P₂, P₃, P₄, P₅, P₆, and P₇ are protective groups, and X₁, X₂, R₂, and R₃ are as described above.

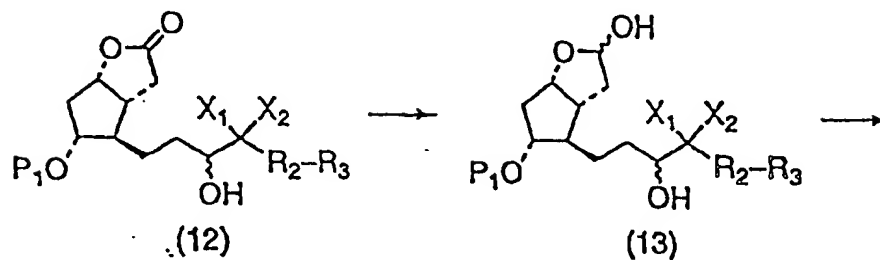
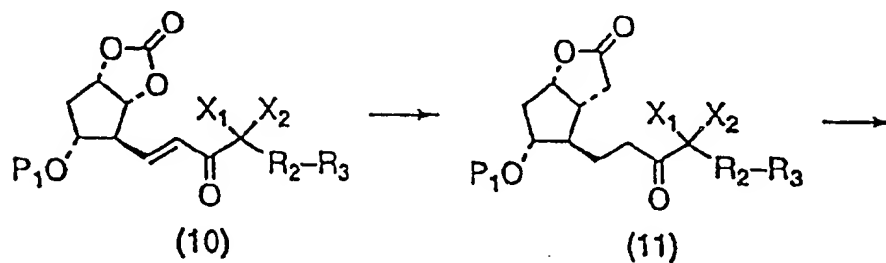
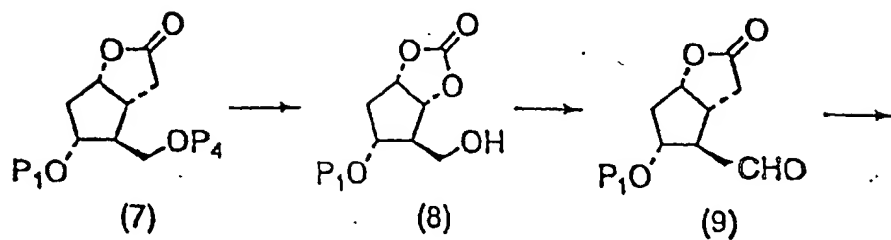
Synthetic Chart 1

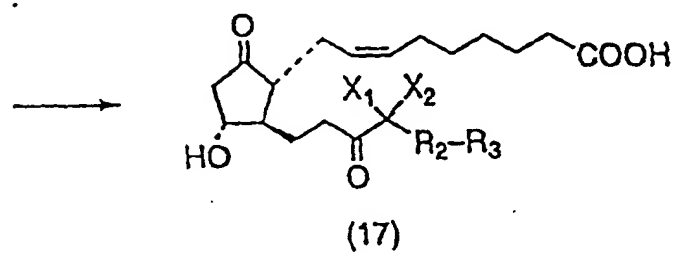
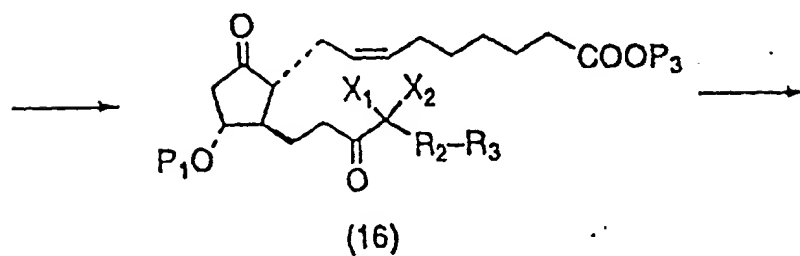
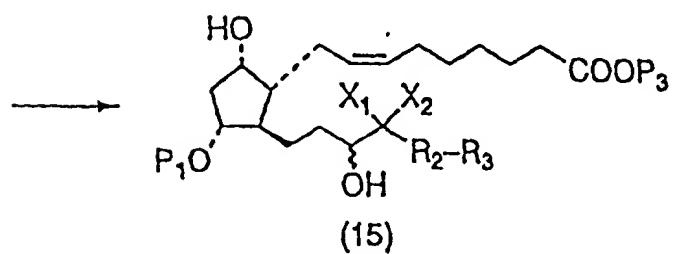
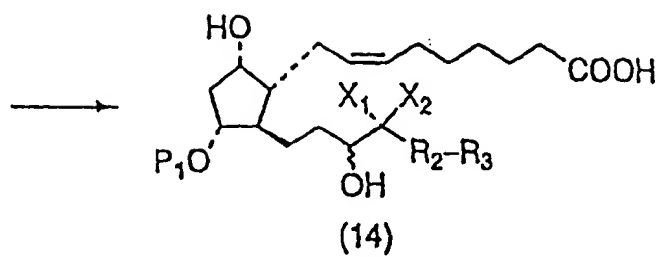


Synthetic Chart 2

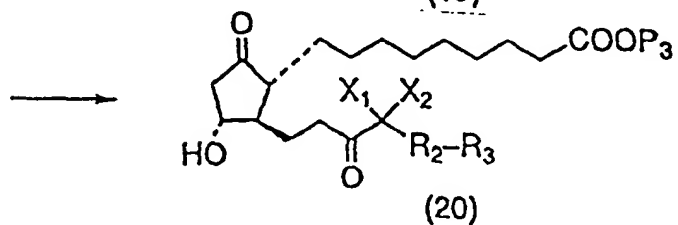
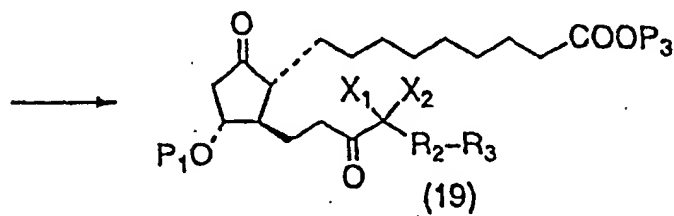
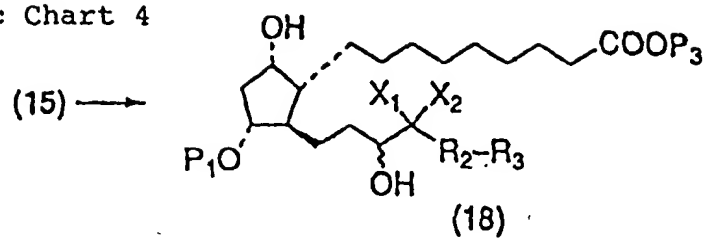


Synthetic Chart 3

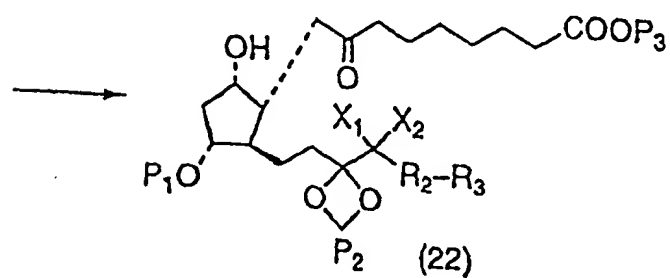
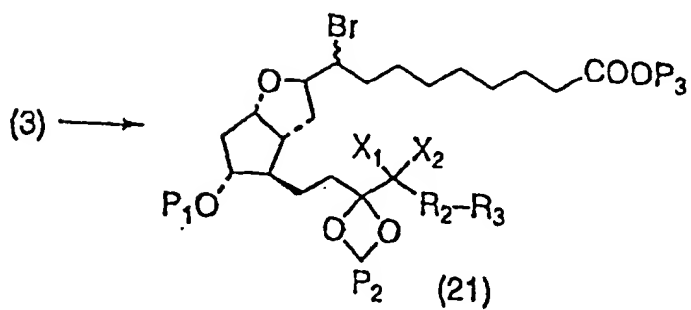




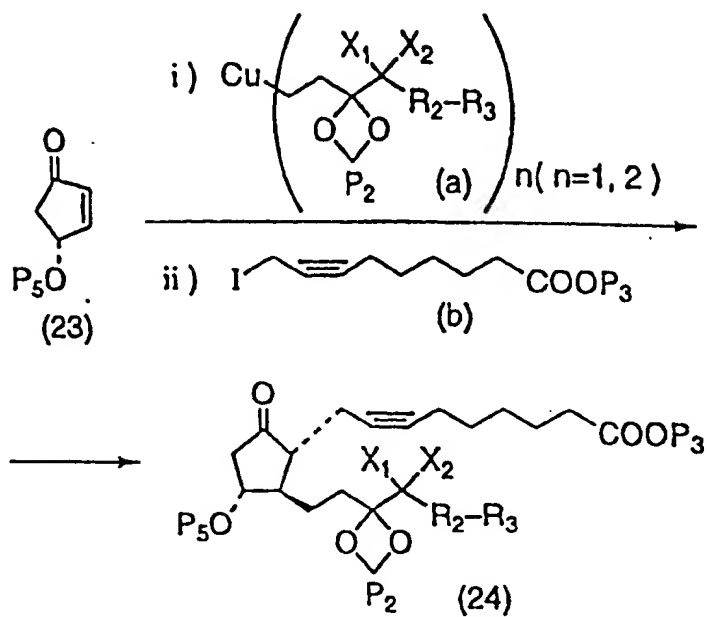
Synthetic Chart 4



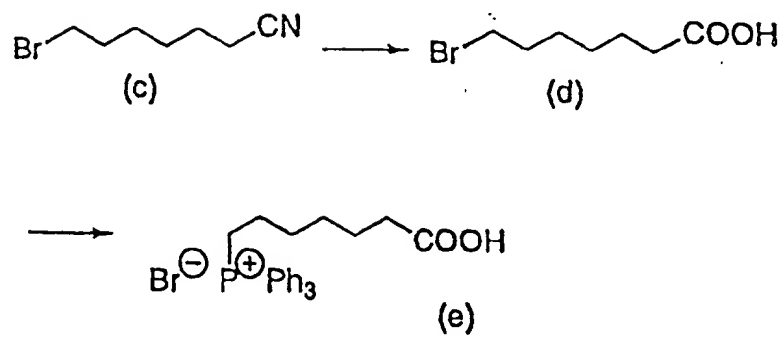
Synthetic Chart 5



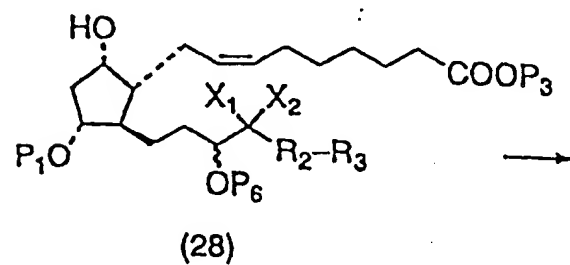
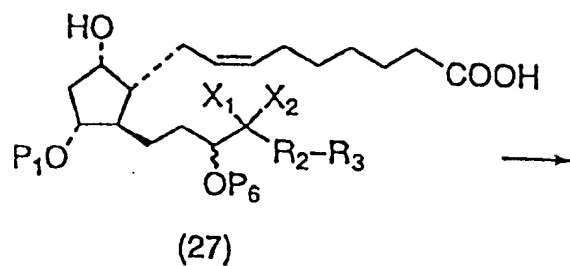
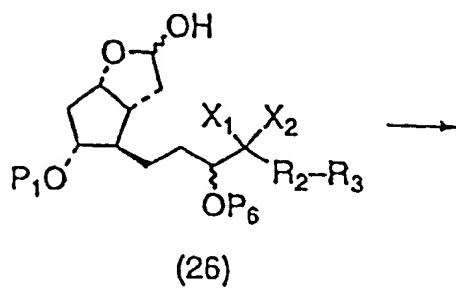
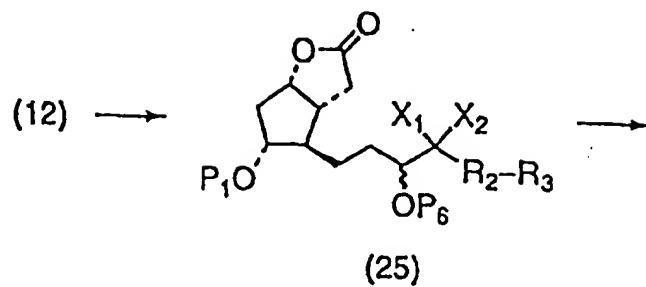
Synthetic Chart 6

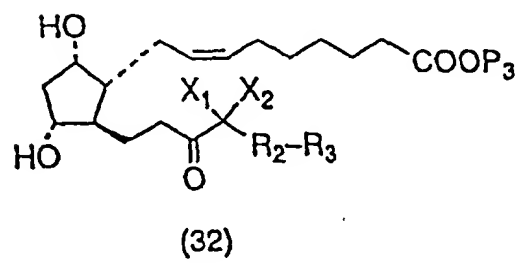
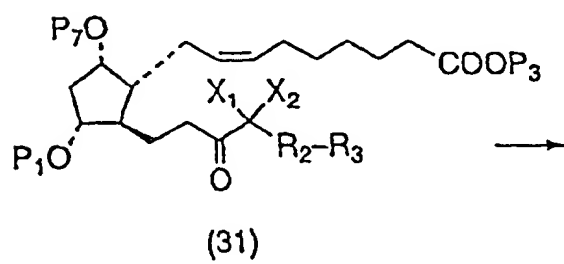
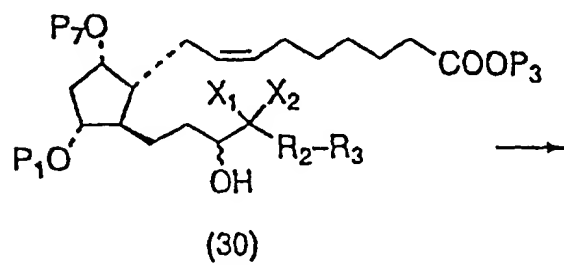
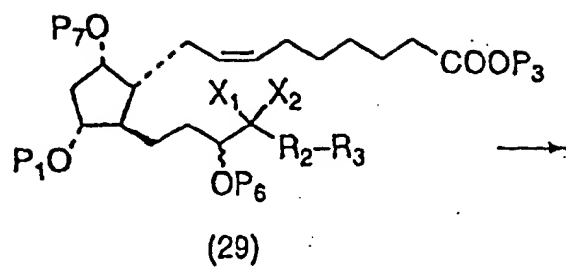


Synthetic Chart 7

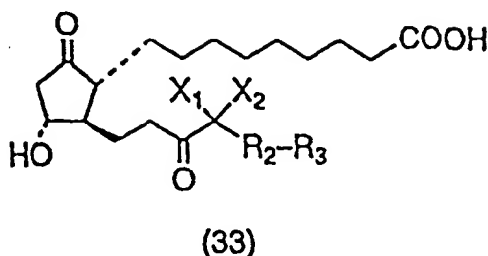


Synthetic Chart 8





Synthetic Chart 9



[0046] In the Synthetic Chart 1, with the compound (1) (wherein, for example, when X_1 and X_2 are hydrogens, respectively, the resulting compound corresponds to the Compound 8 shown in the Synthesis Chart I in page 37 of Japanese Patent Kokai Sho 64-52753) is reacted ylide obtained from (6-carboxyhexyl)triphenyl phosphonium bromide to produce the compound (2), it is esterified to obtain the compound (3), and the protective groups are removed therefrom to obtain the target compound (4). Furthermore, in the Reaction Formula 2, the above described compound (3) is subjected to Jones oxidation to prepare the compound (5), and from which are removed the protective groups to obtain the compound (6).

[0047] As another example, in the Synthetic Chart 3, the compound (8) prepared from the compound (7) (commercially available product) as a result of removing a protective group is subjected to Swan oxidation to produce the aldehyde-form (9), and with which is reacted 2-oxoheptyl phosphonate (e.g., 3,3-dihalo-form) to obtain the compound (10). The resulting compound (10) is catalytically reduced to prepare the compound (11), the ketone thereof is reduced with sodium hydrogenated boron to produce the compound (12), and is reduced with hydrogenated diisobutyl aluminum to obtain lactol (13). With which is reacted carboxyhexyl phosphonium bromide to prepare the compound (14), esterified to produce the compound (15), oxidized to produce the compound (16), and from which is removed a protective group to obtain the compound (6). If desired, the protective group for carboxyl group is removed to obtain the free acid (17). Moreover, in the Synthetic Chart 4, the above described compound (15) is catalytically reduced to prepare the compound (18), it is subjected to Swan oxidation to produce the compound (19), and from which is removed a protective group, whereby the target compound (20) can be obtained.

[0048] In the above described manufacturing methods, when the reduction by which the compound (1) is obtained from the compound (10) is omitted, a compound wherein B is $-\text{CH}=\text{CH}-$ is obtained.

[0049] In the general formula (I), when such compound is a target compound wherein M is a group other than OH (for example, a C_{1-6} alkyl), lactone of the compound (12) wherein 11-position is released from the protection, while 15-position is protected is reduced to lactol, into which is introduced α -chain in accordance with Wittig reaction, the hydroxy group at 11-position is protected by, for example, a C_{1-6} alkane or a monocyclic aryl sulfonic acid group, then, is oxidized (for example, Jones oxidation) to obtain 10-en-9-on, and with which is reacted, for example, a C_{1-6} alkyl copper complex to prepare 11- C_{1-6} alkyl-form. PGD-type compounds are obtained by oxidation of the 11-nonprotective form, while PGA-type compounds are obtained from the 10-en-9-on form. Furthermore, 6-keto compound is obtained in such a manner, for example, as shown in the Synthetic Chart 5 that N-bromsuccinimide or iodine is reacted with the compound (3) to produce the compound (21), and the resulting compound is treated with DBU. 5,6-dehydro compound (i.e., acetylene-form) is obtained in such a manner, for example, as shown in the Synthetic Chart 6 that with a copper enolate prepared by reacting a copper complex with the compound (23) is reacted 8-alkoxycarbonyl-1-iodo-2-octene. A saturated α -chain introducing agent is manufactured, for example, in accordance with the Synthetic Chart 7.

[0050] Furthermore, as another example, in the Synthetic Chart 8, the hydroxyl group at 15-position of the compound (12) is protected (by, for example, a silyl protective group) to prepare the compound (25), the lactone is reduced to lactol to obtain the compound (26), and with which is reacted an α -chain introducing agent, for example, an ylide prepared from (6-carboxyhexyl)triphenyl phosphonium bromide to obtain the compound (27). Then, the carboxyl group is protected to obtain the compound (28), the hydroxyl group at 9-position thereof is protected to prepare the compo-

sition (29), from the 15-position thereof the protective group is removed to obtain the compound (30), oxidized to produce the compound (31), and then, when from the 9- and 11-positions thereof are removed the protective groups, the target compound (32) is obtained.

[0051] Moreover, in the Synthetic Chart 9, the compound (14) in the Synthetic Chart 3 is protected by a protective group which can be removed by catalytic reduction (for example, benzyl) to prepare the compound (15), the 9-position thereof is oxidized, then, from the 11-position thereof is removed the protective group to obtain the compound (6), and when the resulting compound is catalytically reduced, a target compound (33) is obtained.

[0052] The above described prostanoid acid compounds containing 8 or more carbon atoms in α -chain are useful as endothelin antagonist.

[0053] The compounds used in the present invention may be utilized as a pharmaceutical for animal and human being, and they may usually be administered systemically or locally in accordance with ophthalmic administration, oral administration, intravenous injection (including drip infusion), subcutaneous injection, intrarectal administration and the like manner. Especially, use in the form of eye drops is useful. Although the dosage varies dependent upon type, age, body weight, symptom to be treated, desired therapeutic effect, administration route, period to be treated or the like of objects such as animal or human being and the like, sufficient effect is ordinarily achieved by usually the dosage of 0.01 to 100 μ g/eye in case of local administration, or the dosage of 0.001 to 500 mg/kg in case of systemical administration in accordance with divided dose into two to four fractions per day or under sustained condition.

[0054] The ophthalmic preparations according to the present invention include ophthalmic solution or ophthalmic ointment and the like. Ophthalmic solution is prepared by either dissolving the active ingredient into sterile aqueous solution, for example, physiological saline, buffer solution and the like, or combining the former with the latter used at the time of administration. The ophthalmic ointment is prepared by mixing the active ingredient with a base.

[0055] The solid composition for oral administration used according to the present invention includes tablet, troche, sublingual tablet, capsule, pill, powder, granule and the like. In such a solid composition, one or more active ingredient (s) is (are) admixed with at least one inactive diluent such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate. According to a conventional procedure, a composition may contain additives other than the inactive diluent, for example, lubricant such as magnesium stearate; disintegrator such as cellulose calcium gluconate; and stabilizer, for example, etherified cyclodextrin such as α -, β -, and γ -cyclodextrin, or dimethyl- α -, dimethyl- β -, trimethyl- β -, and hydroxypropyl- β -cyclodextrin, branched cyclodextrin such as glycosyl-, maltosyl-cyclodextrin, formylated cyclodextrin, sulfur-containing cyclodextrin, misoprotol (phonetic), and phospholipid. When any of the above described cyclodextrins is used, there is a case where a clathrate inclusion compound is formed from the cyclodextrin to increase the stability of a composition. Furthermore, there is a case when liposome is formed by utilizing phospholipid, the stability of the resulting product increases. If desired, tablet or pill may be covered or coated with a film or two or more layers made of a substance soluble in ventriculus or intestine such as saccharose, gelatin, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose phthalate. Furthermore, a composition may be formed in capsule by the use of a disintegrable material such as gelatin. In case of requiring fast-acting property, a composition may be formed in sublingual tablet.

[0056] As a base, glycerin, lactose and the like may be used. An example of liquid compositions for oral administration includes emulsion, solution, suspension, syrup, and elixir formulations. They may contain an inactive diluent used ordinarily such as purified water, and ethanol. Any of these compositions may further contain an additive such as wetting agent, and suspending agent; edulcorant; flavoring material, aromatic, and preservative in addition to the inactive diluents.

[0057] As another composition for oral administration, there is a spraying agent containing one or more active ingredient(s) and being formulated in accordance with a manner which itself has been well known.

[0058] An example of parenteral solutions according to the present invention includes sterile aqueous or nonaqueous solution, suspension, and emulsion. An example of media for the aqueous solution and the suspension includes distilled water for injection, physiological saline, and Ringer solution.

[0059] An example of diluent for the nonaqueous solution and the suspension includes propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol, polysorbate and the like. These compositions may further contain adjuvants such as preservative, wetting agent, emulsion, and dispersant. They are sterilized by, for example, filtration passing them through a bacteria remaining filter, incorporation of a bactericide, gas sterilization, or radiation sterilization. They may also be manufactured in the form of a sterile solid composition, and it is dissolved in sterile water or a sterile solvent for injection prior to the application therefor.

[0060] Another form for such compositions is suppository or vaginal suppository. These suppositories may be prepared by admixing an active ingredient with a base such as cacao butter or the like which softens at body temperature, and in this case, a nonionic surfactant having a suitable softening temperature may be added further to improve the absorption thereof.

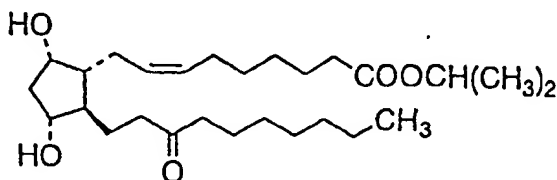
Example

[0061] Although the present invention will be explained in detail by the following examples of syntheses and tests, they do not limit the invention.

Synthesis example 1

Preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-20-ethyl-PGF₂α isopropyl ester [IUPAC name: isopropyl (Z)-9-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-7-nonenoate](4-a)

[0062]



(4-a)

Preparation of raw material compound

(6-carboxyhexyl)triphenylphosphonium bromide (e):

[0063] 7-Bromoheptane nitrile (c) (10.0g) was added to 40% hydrobromic acid (80 ml), and refluxed for 6 hours. The product was extracted with ether after dilution with water. The crude product obtained by the conventional treatment was purified on the silica gel column to give 7-bromoheptanoic acid(d) [yield:7.60g (69%)].

[0064] (6-Carboxyhexyl)triphenylphosphonium bromide(e) was obtained from 7-bromoheptanoic acid(d) (7.60g) and triphenylphosphine (10.0g) [yield:16.0g (93%)].

Preparation of object compound

1-1)(Z)-9-[(1R,2R,3R,5S)-2-(3,3-ethylene dioxydecyl)-5-hydroxy-3-tetrahydropyranyloxy)cyclopentyl]-7-nonenoic acid(2-a)

[0065] Dimethyl sulfoxide (DMSO)(10 ml) was added to sodium hydride (60%;0.422g) which was washed with hexane under argon atmosphere, and the mixture was maintained at 60°C for 3 hours and then cooled to room temperature. (6-Carboxyhexyl)triphenyl-phosphonium bromide (2.49g) was added to the mixture and the resultant mixture was agitated for 30 minutes. The solution of [1S,3(R,S),5R,6R,7R]-6-(3,3-ethylene dioxydecyl)-7-tetrahydropyranyloxy-2-oxabicyclo [3.3.0] octane-3-ol (1-a) in DMSO (11ml) was added to the reaction mixture. The resultant mixture was agitated at room temperature for 2 hours and at 45°C for 1 hour, and then ice-water was poured into the reaction mixture. The titled compound (2-a) was obtained by the conventional treatment of the reaction mixture (yield:1.68g).

1-2)Isopropyl (Z)-9-[(1R,2R,3R,5S)-2-(3,3-ethylene dioxydecyl)-5-hydroxy-3-(tetrahydropyranyloxy)cyclopentyl]-7-nonenoate (3-a)

[0066] The compound (2-a)(1.68g) in acetonitrile (15ml) was esterified with 1,8-diazabicyclo [5.4.0]-7-undecene (DBU)(0.78ml) and isopropyl iodide (0.35ml) by the conventional manner to give the titled compound (3-a). The product was purified on silica gel column (yield:0.908g(88%).

1-3)Isopropyl (Z)-9-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-7-nonenoate (4-a)

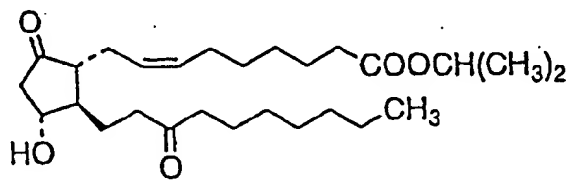
[0067] The compound (3-a)(0.305g) was dissolved in the solvent mixture (acetic acid:THF:water=2:1:1)(6ml) and the solution was maintained at 50°C for 14 hours. The crude product obtained by the conventional treatment was purified on silica gel column to give the titled compound (4-a)[yield:0.213g(90%)].

[0068] Compound (4-a)[compound (4) wherein $X_1=X_2=H$, $R_2-R_3=hexyl$, $P_3=isopropyl$]

NMR($CDCl_3$) δ : 0.85(t, 3H, $J = 6.5Hz$), 1.20(d, 6H, $J = 6Hz$), 1.23~2.65(m, 34H) 3.86(m, 1H), 4.16(m, 1H), 4.99(Hept, 1H, $J = 6Hz$), 5.39(m, 2H)

Synthesis example 2

Preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-20-ethyl-PGE₂ isopropyl ester [IUPAC name: isopropyl (Z)-9-[(1R,2R,3R)-3-hydroxy-5-oxo-2-(3-oxodecyl)cyclopentyl]-7-nonenoate](6-a)



(6-a)

2-1)isopropyl (Z)-9-[(1R,2R,3R)-2-(3,3-ethylene dioxydecyl)-5-oxo-3-(tetrahydropyranyloxy)cyclopentyl]-7-nonenoate (5-a)

[0070] Oxalyl chloride (2M;0.45ml) and DMSO(0.13ml) were added to dichloromethane (5ml) which was previously cooled to $-70^{\circ}C$ and the mixture was agitated for 15 minutes. The solution of isopropyl (Z)-9-[(1R,2R,3R,5S)-2-(3,3-ethylene dioxydecyl)-5-hydroxy-3-(tetrahydropyranyloxy)cyclopentyl]-7-nonenoate (3-a)(0.350g) in dichloromethane (7ml) was dropped into the mixture. The resultant mixture was warmed to $-55^{\circ}C$ and agitated for 15 minutes, and then triethylamine (0.25ml) was added to the mixture. The resultant mixture was warmed to $10^{\circ}C$ over 6 hours. The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the titled compound (5-a)[yield:0.311g(89%)].

2-2)isopropyl (Z)-9-[(1R,2R,3R)-3-hydroxy-5-oxo-2-(3-oxodecyl)cyclopentyl]-7-nonenoate (6-a)

[0071] The compound (5-a)(0.311g) was dissolved in the solvent mixture (acetic acid:THF:water=2:1:1)(5ml) and the solution was maintained at $50^{\circ}C$ for 3 hours. The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the titled compound (6-a)[yield:0.156g(66%)].

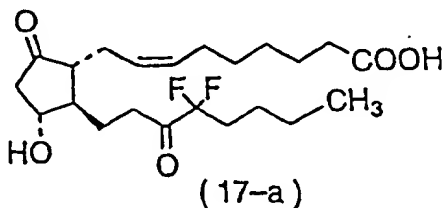
[0072] Compound (6-a) [compound (6) wherein $X_1=X_2=H$, $R_2-R_3=hexyl$, $P_3=isopropyl$]

NMR($CDCl_3$) δ : 0.86(t, 3H, $J = 6.5Hz$), 1.20(d, 6H, $J = 6Hz$), 1.23~2.75(m, 33H), 4.20(m, 1H), 4.99(Hept, 1H, $J = 6Hz$), 5.15~5.50(m, 2H)

Synthesis example 3

Preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-PGE₂ [IUPAC name:(Z)-9-[(1R,2R,3R)-2-(4,4-difluoro-3-oxooctyl)-3-hydroxy-5-oxocyclopentyl]-7-nonenoic acid](17-a)

[0073]



(17-a)

3-1) (1S,5R,6R,7R)-6-(4,4-difluoro-3-oxooctenyl)-7-tetrahydropyranyloxy)-2-oxabicyclo [3,3,0] octane-3-one (10-a)

[0074] (1S,5R,6R,7R)-6-Hydroxymethyl-7-(tetrahydropyranyloxy)-2-oxabicyclo [3,3,0] octane-3-one (8-a) (27.8g) prepared from the commercially available (1S,5R,6R,7R)-6-(t-butyltrimethyl silyloxymethyl)-7-(tetrahydropyranyloxy)-2-oxabicyclo [3,3,0] octane-3-one (7-a) was subjected to Swan oxidation with oxalyl chloride (2.0M;109.3ml), DMSO (31.0ml) and triethylamine (150ml) in dichloromethane (800ml) to give the compound (9-a) (P₁=tetrahydropyranyl).

[0075] The compound (9-a) was reacted with dimethyl-3,3-difluoro-2-oxoheptylphosphonate (30.0g) in dichloromethane in the presence of thallium methoxide (8.23ml). The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the titled compound (10-a) [yield:24.4g(58%)].

3-2) (1S,5R,6R,7R)-6-(4,4-difluoro-3-oxooctyl)-7-tetrahydropyranyloxy)-2-oxabicyclo [3,3,0] octane-3-one (11-a)

[0076] The compound (10-a) (12.7g) in ethyl acetate (300ml) was catalytically reduced with catalytic amount of 5% Pd-C and hydrogen gas to give the titled compound (11-a) [yield:12.5g(99%)].

3-3) (1S,5R,6R,7R)-6-[4,4-difluoro-3(R,S) hydroxyoctyl]-7-tetrahydropyranyloxy)-2-oxabicyclo [3,3,0] octane-3-one (12-a)

[0077] The compound (11-a) (12.6g) in methanol (400ml) was reduced with sodium borohydride (1.25g) at 0°C to obtain the titled compound (12-a) [yield:12.1g(95.5%)].

3-4) [1S,3(R,S)5R,6R,7R)-6-[4,4-difluoro-3(R,S)-hydroxyoctyl]-7-(tetrahydropyranyloxy)-2-oxabicyclo [3,3,0] octane-3-ol (13-a)

[0078] The compound (12-a) (12.1g) in toluene (500ml) was reduced with diisobutyl aluminum hydride (1.5M;65.1ml) at -78°C, and the product was purified on silica gel column to give the titled compound (13-a) [yield:11.1g(91%)].

3-5)phenacyl (Z)-9-((1S,2R,3R,5S)-2-[4,4-difluoro-3(RS)- hydroxyoctyl]-5-hydroxy-3-tetrahydropyranyloxy)cyclopentyl]-7-nonenolate (15-a)

[0079] DMSO (40ml) was added to sodium hydride (60%;1.63g) which was washed with pentane, and the mixture was maintained at 65-70°C for 1.5 hours and cooled to room temperature. (6-Carboxyhexyl)triphenylphosphonium bromide (e) (9.61g) was added to the mixture to form ylide. The solution of the compound (13-a) (2.00g) in DMSO (15ml) was dropped to the ylide, and the mixture was held overnight at room temperature. The compound (14-a) was obtained by the conventional treatment of the product [yield:3.18g(crude product)].

[0080] The compound (14-a) (0.795g), phenacyl bromide (1.01g) and diisopropylethylamine (0.89ml) were dissolved in acetonitrile (10ml), and the solution was maintained at room temperature for 20 minutes and at 45°C for 30 minutes. The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the titled compound (15-a) [yield:0.604g].

3-6)phenacyl (Z)-9-((1S,2R,3R)-2-(4,4-difluoro-3-oxooctyl)-5-oxo-3-(tetrahydropyranyloxy)cyclopentyl]-7-nonenolate (16-a)

[0081] DMSO (0.92ml) was dropped to the solution of oxalyl chloride (0.52ml) in dichloromethane (30ml) which was cooled to -78°C. The solution of the compound (15-a) (0.609g) in dichloromethane (15ml) was added to the mixture, and the resultant mixture was agitated at -30°C- -20°C for 1.5 hours. Triethylamine (1.88ml) was added to said mixture, and the resultant mixture was agitated for 30 minutes. The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the titled compound (16-a) [yield:0.514g(85%)].

3-7)phenacyl (Z)-9- [(1R,2R,3R)-2-(4,4-difluoro-3-oxooctyl)-3-hydroxy-5-oxocyclopentyl]-7-nonenolate (16-b)

[0082] The compound (16-a)(0.514g) was dissolved in the solvent mixture (acetic acid:water:THF=4:2:1)(30ml), and the solution was maintained overnight at room temperature. The titled compound (16-b) was obtained by purifying the crude product on silica gel column [yield:0.272g(61%)].

[0083] Compound (16-b)[compound (6) wherein X₁=X₂=F, R₂-R₃=butyl, P₃=phenacyl]

NMR(CDCl₃) δ : 0.92(t,3H, J=7.5Hz), 1.2-2.9(m, 27H), 4.18(m, 1H), 5.4 (m, 2H), 7.4-8.0 (m, 5H)

3-8) (Z)-9-[(1R,2R,3R)-2-(4,4-difluoro-3-oxooctyl)-3-hydroxy-5-oxocyclopentyl]-7-nonenoic acid (17-a)

[0084] The compound (16-b)(0.272g) was dissolved in acetic acid (10ml). Zinc (3.5g) was added little by little at room temperature, and the mixture was agitated for 2.5 hours. The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the titled compound (17-a) [yield:0.177g(81%)].

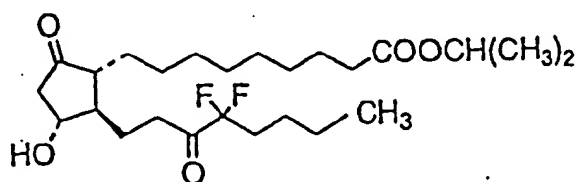
[0085] Compound (17-a)[compound (17) wherein $X_1=X_2=F$, R_2-R_3 =butyl]

NMR($CDCl_3$) δ : 0.93(t, 3H, J = 6.5Hz), 1.15~2.9 5(m, 28H), 4.19(m, 1H), 5.36(m, 1H)

Synthesis example 4

Preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-PGE₁ isopropyl ester [IUPAC name:isopropyl 9-[(1R,2R,3R)-2-(4,4-difluoro-3-oxooctyl)-3-hydroxy-5-oxocyclopentyl]-nonanoate(20-a)]

[0086]



(20-a)

4-1)isopropyl (Z)-9-[(1R,2R,3R,5S)-2-[4,4-difluoro-(3RS)- hydroxyoctyl]-5-hydroxy-3-(tetrahydropyranyloxy)cyclopentyl]-7-nonenoate (15-b)

[0087] The compound (14-a) prepared in synthesis example 3 (0.802g), DBU(0.76ml) and isopropyl iodide (0.51ml) were dissolved in acetonitrile (15ml), and the solution was maintained at 50°C for 1 hour. The compound (14-a) (0.492g) was further reacted in similar manner to give the titled compound (15-b) [yield:0.315g(total)].

4-2)isopropyl 9-[(1R,2R,3R)-2-[4,4-difluoro-(3RS)-hydroxyoctyl]-5-hydroxy-3-(tetrahydropyranyloxy)cyclopentyl]-nonanoate (18-a)

[0088] The compound (15-b) (0.315g) in ethanol (20ml) was catalytically reduced with 5% Pd-C (0.08g) and hydrogen gas to give the titled compound (18-a) [yield:0.301g(95%)].

4-3)isopropyl 9-[(1R,2R,3R)-2-(4,4-difluoro-3-oxooctyl)-5-oxo-3-(tetrahydropyranyloxy)cyclopentyl]-nonanoate (19-a)

[0089] The compound (18-a)(0.301g) in dichloromethane was subjected to Swan oxidation with oxalyl chloride (0.34ml), DMSO (0.61ml) and triethylamine (1.22ml) to give the titled compound (19-a)[yield:0.288g(96%)].

4-4)isopropyl 9-[(1R,2R,3R)-2-(4,4-difluoro-3-oxooctyl)-3-hydroxy-5-oxocyclopentyl]nonanoate (20-a)

[0090] The compound (19-a)(0.288g) was dissolved in the solvent mixture (acetic acid:water:THF=4:2:1)(30ml), and the solution was maintained at 45°C for 3.5 hours. The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the titled compound (20-a) [yield:0.184g(76%)].

[0091] Compound (20-a) [compound (20) wherein $X_1=X_2=F$, R_2-R_3 =butyl, P_3 =isopropyl]

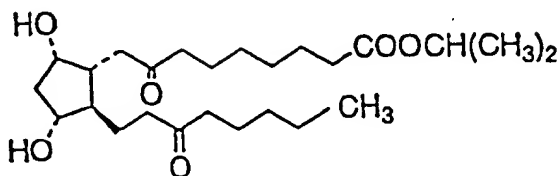
NMR($CDCl_3$) δ : 0.94 (t, 3H, J = 6.5Hz), 1.24(d, 6H, J = 6Hz), 1.27~2.95(m, 31H), 4.19(m, 1H), 5.02(Hep t, 1H, 3 = 6Hz)

[0092] The compound (I) wherein Y is -CO-CH₂- or -C \equiv C- can be prepared by the following manner.

Synthesis example 5

Preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-6,15-diketo-PGF₁α isopropyl ester (22-a)

[0093]



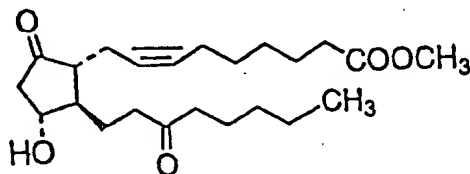
(22-a)

[0094] The compound (3-a) prepared in synthesis example 1 was dissolved in the mixture of tetrahydrofuran and methylene chloride, and a small excess amount of N-bromosuccinimide was added and agitated at 0°C for 5 minutes. The crude product obtained by the conventional post-treatment of the reaction mixture was purified by column chromatography to obtain the compound (21-a) [compound (21) wherein X₁=X₂=H, R₂-R₃=butyl, P₁=tetrahydropyranyl, P₂=ethylene, P₃=isopropyl]. Said compound was dissolved in toluene, and DBU was added to the solution. The mixture was agitated overnight at 40°C. The reaction mixture was cooled with ice, acidified with 1N-HCl, agitated for 10 minutes and then extracted with ethyl acetate. The compound (22-b) [compound (22) wherein X₁ and the like have the same meanings as defined above] was obtained by purifying the crude product by means of column chromatography, said crude product being obtained by the conventional post-treatment of the reaction mixture. Said compound was subjected to the same deprotection treatment as in the process of 1-3) in the synthesis example 1 to give the titled compound (22-a).

Synthesis example 6

Preparation of 2-decarboxy-2-(2-carboxyethyl)-5,6-dehydro-13,14-dihydro-15-keto-PGE₂ methyl ester (24-a)

[0095]



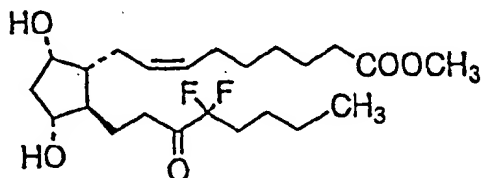
(24-a)

[0096] Tertiary butyllithium was dropped to the solution of 8-methoxy-3,3-ethylenedioxy-1-iodooctane (cf. Japanese Patent Publication (KOKAI) No. 52753/1989) in ether over 30 minutes, and the mixture was agitated for 3 hours. The solution of tributyl phosphine and cuprous iodide in ether which was cooled to -78°C was added at once to the reaction mixture. The resultant mixture was agitated for 20 minutes to produce the complex (a). The solution of 4R-tertiary butyldimethylsilyloxy-2-cyclopentene-1-one (23-a) in tetrahydrofuran was dropped to the reaction mixture over 95 minutes, and the resultant mixture was agitated for 15 minutes and then cooled with the cooling bath (-30°C). The solution of 8-methoxycarbonyl-1-iodooctane (b) in HMPA was added to said cooled mixture, and the resultant mixture was agitated for 4.5 hours and then agitated at room temperature for 12 hours. The reaction mixture was poured into the aqueous saturated solution of ammonium chloride, and the resultant organic layer was separated. The crude product obtained by the conventional post-treatment of the organic layer was purified by chromatography to give the compound (24-b) [compound (24) wherein X₁=X₂=H, R₂-R₃=butyl, P₃=methyl, P₅=tertiary butyldimethylsilyl]. Said compound was deprotected by the ordinary manner to give the titled compound (24-a).

Synthesis example 7

Preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-PGF₂α methyl ester [IUPAC name:methyl (Z)-9-[(1R,2R,3R,5S)-2-(4,4-difluoro-3-oxooctyl)-3,5-dihydroxycyclopentyl]-7-nonenoate(32-a)]

[0097]



(32-a)

7-1) [1S,3(R,S),5R,6R,7R]-6-[3(R,S)-t-butyldimethylsilyloxy-4,4-difluorooctyl]-7-tetrahydropyranyloxy-2-oxabicyclo [3.3.0] octane-3-ol (26-a)

[0098] The compound (12-a) [compound (12) wherein $X_1=X_2=F$, P_1 =tetrahydropyranyl, R_2-R_3 =butyl](1.26g) in DMF (15ml) was converted into silylether (25-a) with imidazole (2.63g) and t-butyldimethylsilane chloride (2.91g)[yield:1.43g (88%)]. The silyl ether (25-a) (1.43g) was reduced with diisobutyl aluminium hydride by the ordinary manner to give the titled compound (26-a) [yield:1.47g(100%)].

7-2)methyl (Z)-9-[(1R,2R,3R,5S)-2-[3(R,S)-t-butyldimethylsilyloxy-4,4-difluorooctyl]-5-hydroxy-3-tetrahydropyranyloxy)cyclopentyl]-7-nonenoate (28-a)

[0099] The ylide was prepared with sodium hydride (60%;0.934g), DMSO (25ml) and (6-carboxyhexyl)triphenylphosphonium bromide (5.50g) by the ordinary manner. The solution of the compound (26-a) in ether (8ml) was added to the reaction mixture, and the resultant mixture was agitated at room temperature for 2 hours. The carboxylic acid (27-a) obtained by the conventional treatment of the reaction mixture was treated with diazomethane, and the treated product was purified on silica gel column to give the titled compound (28-a) [yield:0.43g(48%)].

7-3)methyl (Z)-9-[(1R,2R,3R,5S)-2-[3(R,S)-t-butyldimethylsilyloxy-4,4-difluorooctyl]-3,5-ditetrahydropyranyloxy)cyclopentyl]-7-nonenoate (29-a)

[0100] The compound (28-a) (0.438g) in dichloromethane (25ml) was converted into ditetrahydropyranyl ether with an excess amount of dihydropyran and a catalytic amount of p-toluenesulfonic acid. Said product was purified on silica gel column to obtain the titled compound (29-a) [yield:0.494g(99%)].

7-4)(Z)-9-[(1R,2R,3R,5S)-2-oxy-4,4-difluoro-3-oxooctyl)-3,5-ditetrahydropyranyloxy)cyclopentyl]-7-methyl nonenoate (31-a)

[0101] The compound (29-a) (0.494g) was dissolved in THF (10ml), and tetrabutylammonium fluoride (1.0M;5.6ml) was added to the solution. The mixture was left overnight at room temperature. The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the deprotected compound (30-a) [yield:0.284g(68%)].

[0102] The compound (30-a) (0.284g) in dichloromethane (10ml) was subjected to Swan oxidation with oxalyl chloride (0.165ml) and DMSO (0.3ml). The titled compound (31-a) was obtained by purifying the crude product on silica gel column [yield:0.251g(89%)].

7-5)methyl (Z)-9-[(1R,2R,3R,5S)-2-(4,4-difluoro-3-oxooctyl)-3,5-dihydroxycyclopentyl]-7-nonenoate (32-a)

[0103] The compound (31-a)(0.251g) was dissolved in the solvent mixture (acetic acid:water:THF=4:2:1)(30ml), and the solution was maintained at 45-50°C for 3 hours. The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the titled compound (32-a) [yield:0.137g(76%)].

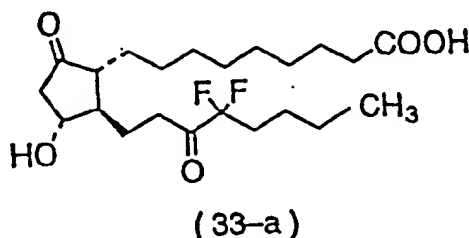
[0104] The compound (32-a) [compound (32) wherein $X_1=X_2=F$, R_2-R_3 =butyl, P_3 =methyl]

NMR(CDCl₃) δ : 0.92(t, 3H, J = 7.5Hz), 1.2-2.9(m, 38H), 3.67(s, 3H), 3.70 (q, 1H, J = 7.5Hz), 4.25 (m, 1H), 5.43 (m, 2H)

Synthesis example 8

Preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-PGE₁ [IUPAC name:9-[(1R,2R,3R,5S)-2-(4,4-difluoro-3-oxooctyl)-3-hydroxy-5-oxocyclopentyl] nonanoic acid (33-a)

[0105]



8-1)benzyl (Z)-9-[(1S,2R,3R,5S)-2-[4,4-difluoro-3(R,S)-hydroxyoctyl]-5-hydroxy-3-(tetrahydropyranyloxy) cyclopentyl]-7-nonenoate (15-c)

[0106] The compound (14-b) [compound (14) wherein X₁=X₂=F, P₁=tetrahydropyranyl, R₂-R₃=butyl] (1.09g) was dissolved in acetonitrile (20ml). DBU (2.6ml) and benzyl bromide (2.2ml) were added to the solution, and the resultant mixture was maintained at 45°C for 1 hour and at 60°C overnight. The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the titled compound (15-c) (yield:0.213g).

8-2)benzyl (Z)-9-[(1R,2R,3R,5S)-2-(4,4-difluoro-3-oxooctyl) -3-tetrahydropyranyloxy)-5-oxocyclopentyl]-7-nonenoate (16-c)

[0107] The compound (15-c) (0.213g) in dichloromethane (15ml) was subjected to Swann oxidation with oxalyl chloride (0.23ml), DMSO (0.41ml) and triethylamine (0.81ml). The titled compound (16-c) was obtained by purifying the crude product on silica gel column [yield:0.181g(86%)].

8-3)benzyl (Z)-9-[(1R,2R,3R,5S)-2-(4,4-difluoro-3-oxooctyl) -3-hydroxy-5-oxocyclopentyl]-7-nonenoate (6-c)

[0108] The compound (16-c)(0.181g) was dissolved in the solvent mixture [acetic acid:water:THF=(4:2:1)](25ml), and the solution was maintained at 45°C for 3.5 hours. The crude product obtained by the conventional treatment of the reaction mixture was purified on silica gel column to give the titled compound (6-c) [yield:0.140g(91%)].

[0109] The compound (6-c) [compound (6) wherein X₁=X₂=F, R₂-R₃=butyl, P₃=methyl]

NMR(CDCl₃) δ : 0.93(t, 8H, 3=7.5Hz), 1.2-2.8(m, 27H), 4.20(m, 1H), 5.12 (s, 2H) , 5.2 -5.5 (m, 2H) , 7.35 (m, 5H)

8-4) 9-[(1R,2R,3R,5S)-2-(4,4-difluoro-3-oxooctyl) -3-hydroxy-5-oxocyclopentyl] nonanoic acid (33-a)

[0110] The compound (6-c) (0.140g) was dissolved in ethyl acetate (15ml), and the solution was subjected to catalytic reduction with Pd-C (50mg) and hydrogen gas. After filtering off the catalyst, the crude product obtained by concentrating the filtrate was purified with Lobar column (ODS) to obtain the titled compound (33-a) [yield:0.077g(65%)].

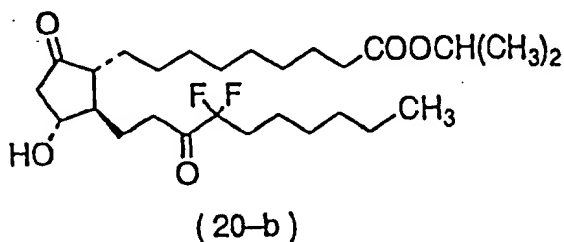
[0111] The compound (33-a) [compound (33) wherein X₁=X₂=F, R₂-R₃=butyl]

NMR(CDCl₃) δ : 0.95(t, 3H, J = 7.5Hz), 1.2-2.8(m, 32H), 4.20(m, 1H)

Synthesis example 9

Preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE₁ isopropyl ester [IUPAC name: isopropyl 9-[(1R,2R,3R)-2-(4,4-difluoro-3-oxodecyl)-3-hydroxy-5-oxocyclopentyl]-nonanoate] (20-b)

[0112]



[0113] The titled compound (20-b) was obtained by the same manner as in the synthesis example 4 with the exception that dimethyl (3,3-difluoro-2-oxononyl) phosphonate was used as alkylphosphonate.

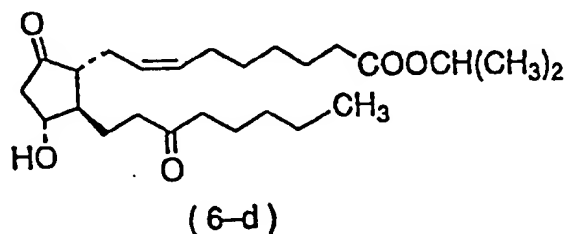
[0114] The compound (20-b) [compound (20) wherein $X_1=X_2=F$, R_2-R_3 =hexyl, P_3 =isopropyl]

NMR (CDCl₃) δ : 0.90 (t, 3H, $J = 7.5$ Hz), 1.32 (d, 6H, 6Hz), 1.25-2.70 (m, 34H), 3.15 (s, 1H), 4.20 (m, 1H), 5.00 (Hept, 1H, 7.5Hz)

Synthesis example 10

Preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-PGE₂ isopropyl ester [IUPAC name: isopropyl (Z)-9-[(1R,2R,3R)-2-(3-oxooctyl)-3-hydroxy-5-oxocyclopentyl]-nonanoate] (6-d)

[0115]



[0116] The titled compound (6-d) was obtained by the same manner as in the synthesis example 2 with the exception that dimethyl (2-oxoheptyl) phosphonate was used as alkylphosphonate.

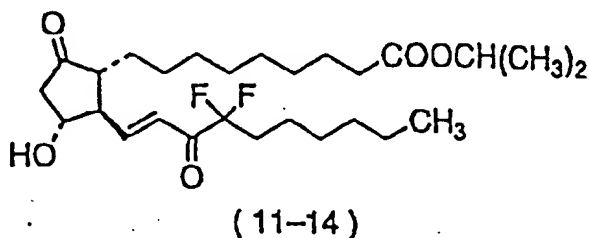
[0117] The compound (6-d) [compound (6) wherein $X_1=X_2=H$, R_2-R_3 =butyl, P_3 =isopropyl]

NMR (CDCl₃) δ : 0.89 (t, 3H, $J = 6.6$ Hz), 1.18 (d, 6H, 6.2Hz), 1.15-3.0 (m, 29H), 4.04 (m, 1H), 4.99 (Hept, 1H, 6.2Hz), 5.37 (m, 2H)

Synthesis example 11

Preparation of isopropyl 9[2(R)-4,4-difluoro-3-oxodece-1-nyl]-3(R)-hydroxy-5-oxocyclopentyl]nonanoate (11-14);
[2-decarboxy-2-(2-carboxyethyl)-15-keto-16,16-difluoro-20-ethyl-PGE₁ isopropyl ester (11-14)

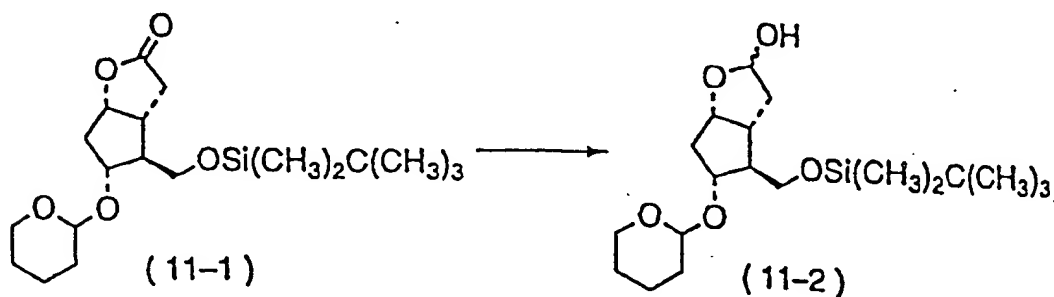
[0118]



11-1)

[1S,3(RS),5R,6R,7R]-6-(t-butyldimethylsiloxymethyl)-7-(tetrahydropyranyloxy)-2-oxabicyclo [3.3.0] octa-3-ol (11-2)

[0119]

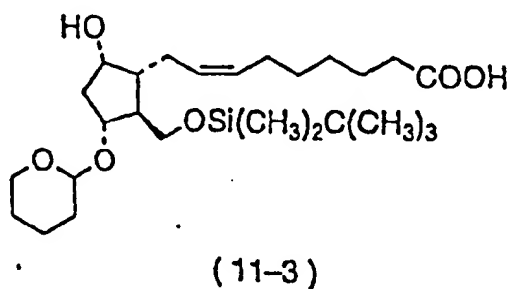


[0120] (1S,5R,6R,7R)-(t-Butyldimethylsiloxymethyl)-7-(tetrahydropyranyloxy)-2-oxabicyclo [3.3.0] octa-3-one (11-1) (2.97g) in toluene was reduced with DIBAL-H (1.6M;1.2ml) at -78°C. The titled compound (11-2) was obtained by the conventional treatment of the reaction product [yield:2.81g(95%)].

11-2)

7(Z)-9-[2(R)-(t-Butyldimethylsiloxymethyl)-5(R)-hydroxy-3(R)-(tetrahydropyranyloxy)cyclopentyl] non-7-enoic acid (11-3)

[0121]

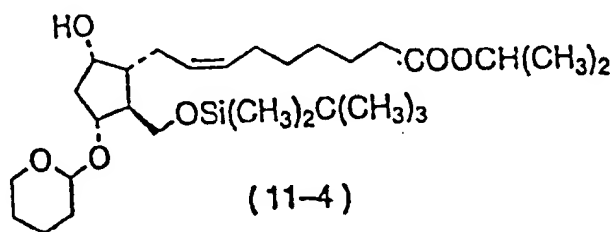


[0122] The solution of lactol (11-2) (2.81g) in THF(10ml) was added to the ylide prepared from the reaction of (6-carboxyhexyl) triphenylphosphonium bromide (10.7g) in THF (28ml) with potassium t-butoxide (1M solution in THF; 45.2ml), and the mixture was agitated overnight at room temperature. The titled compound (11-3) was obtained by the conventional treatment of the reaction product (yield:6.90g).

11-3)

Isopropyl 7(Z)-9-[2(R)-(t-butyldimethylsiloxymethyl)-5(R)-hydroxy-3(R)-(tetrahydropyranyloxy)cyclopentyl] non-7-enoate (11-4)

[0123]

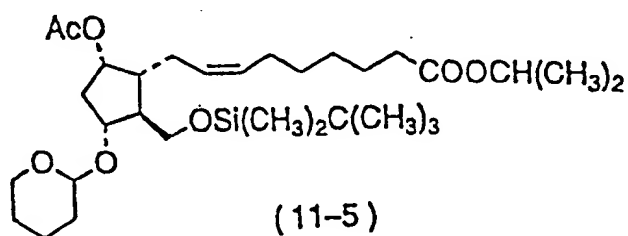


[0124] Carboxylic acid (11-3) (6.90g) in acetonitrile (35ml) was converted into isopropyl ester with isopropyl iodide (2.25ml) and DBU (3.38ml). The crude product obtained by the conventional treatment of the reaction mixture was purified by silica gel chromatography (n-hexane/ethyl acetate=5/1-3/1) to obtain the titled isopropyl ester (11.4) [yield: 3.29g(77%; 3 reaction processes)].

11-4)

Isopropyl 7(Z)-9-[5(R)-(acetoxymethyl)-2(R)-(t-butyldimethylsiloxymethyl)-3(R)-(tetrahydropyranyloxy)cyclopentyl]non-7-enoate (11-5)

[0125]

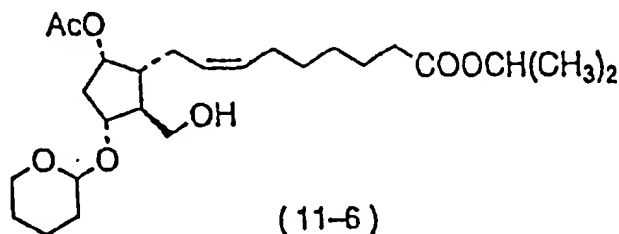


[0126] The compound (11-4) (3.29g) in dichloromethane was acetylated with dimethylaminopyridine (1.84g) and acetic anhydride (1.84g). The titled compound (11-5) was obtained by the conventional treatment of the reaction mixture (yield:3.79g).

11-5)

Isopropyl 7(Z)-9-[5(R)-(acetoxymethyl)-2(R)-hydroxymethyl)-3(R)-(tetrahydropyranyloxy)cyclopentyl] non-7-enoate (11-6)

[0127]

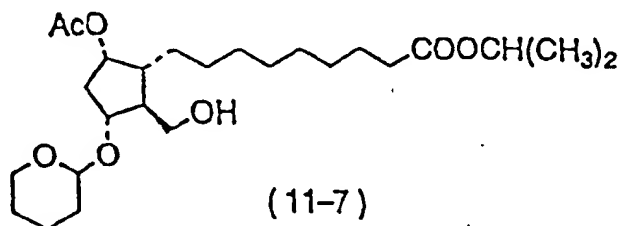


[0128] Tetrabutylammonium fluoride [1.0M (THF solution); 7.5ml] was added to the compound (11-5) (3.79g) in THF (50ml), and the mixture was agitated overnight at room temperature. The crude product obtained by the conventional treatment of the reaction mixture was purified by silica gel chromatography (n-hexane/ethyl acetate=3/2-2/3) to give the titled compound (11-6) [yield: 2.91g (83%)].

11-6)

Isopropyl 9-[5(R)-(acetoxymethyl)-2(R)-hydroxymethyl)-3(R)-(tetrahydropyranyloxy)cyclopentyl]nonanoate (11-7)

[0129]

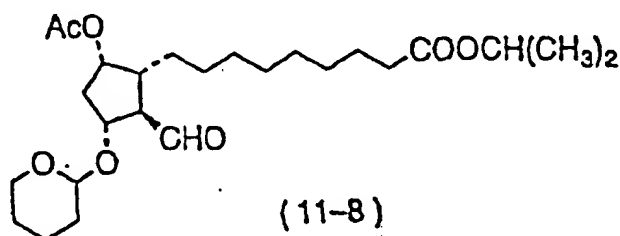


[0130] The compound (11-6) (2.84g) in ethyl acetate (20ml) was subjected to catalytic reduction with 5% Pd-C (0.284g) and hydrogen gas at room temperature. The crude product was purified by silica gel chromatography (n-hexane/ethyl acetate=1/1 ethyl acetate) to give the titled compound (11-7) [yield: 2.34g (82%)].

11-7)

Isopropyl 9-[5(R)-(acetoxymethyl)-2(R)-formyl-3(R)-(tetrahydropyranyloxy)cyclopentyl]nonanoate (11-8)

[0131]



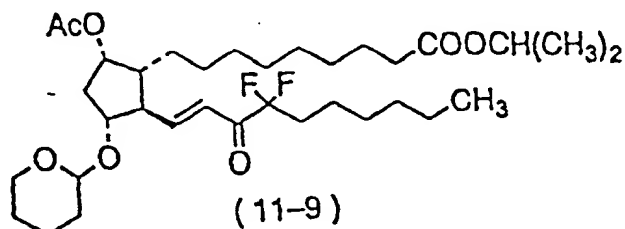
[0132] The compound (11-7) (2.34g) in dichloromethane (-78°C) was subjected to Swann oxidation with oxalyl chloride

[2M(CH₂Cl₂ solution);1.2ml], DMSO(0.34ml) and triethylamine (2.5ml). The titled compound (11-8) was obtained by the conventional treatment of the reaction mixture.

11-8)

Isopropyl 9-[5(R)-(acetoxo)-2(R)-(4,4-difluoro-3-oxodece-1-nyl)-3(R)-(tetrahydropyranyloxy)cyclopentyl] nonanoate (11-9)

[0133]

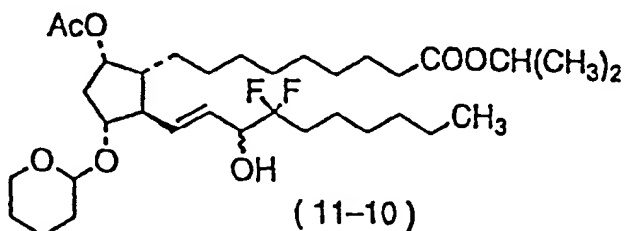


[0134] Sodium hydride (60%;0.096g) was suspended in THF (4ml) at 0°C, and the solution of dimethyl (3,3-difluoro-2-oxononyl)phosphonate (1.03g) in THF(4ml) was added to the suspension. The mixture was agitated for 20 minutes, and the solution of the compound (11-8) in THF (6ml) was dropped to said mixture. The resultant mixture was refluxed overnight. The crude product obtained by the conventional treatment of the reaction mixture was purified by silica gel chromatography (n-hexane/ethyl acetate=9/1-17/3) to give the titled compound (11-9) [yield:0.51g(69%)].

11-9)

Isopropyl 9-[5(R)-(acetoxo)-2(R)-[4,4-difluoro-3-(RS)-hydroxydece-1-nyl]-3(R)-(tetrahydropyranyloxy)cyclopentyl] nonanoate (11-10)

[0135]

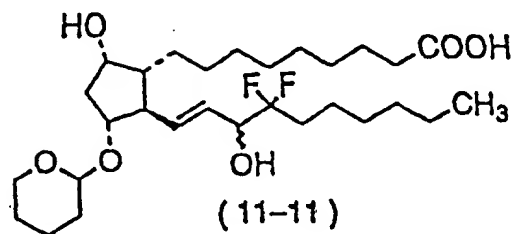


[0136] The compound (11-9) (0.51g) was reduced with zinc borohydride prepared by the reaction of sodium borohydride (0.19g) and zinc chloride (0.34g) in ether (8ml). The crude product obtained by the conventional treatment of the reaction mixture was purified by silica gel chromatography (n-hexane/ethyl acetate=4/1-3/1) to give the titled compound (11-10) [yield:0.47g(93%)].

11-10)

9-[5(R)-[4,4-difluoro-3-(RS)-hydroxydece-1-nyl]-5(R)-hydroxy-3(R)-tetrahydropyranyloxy)cyclopentyl] nonanoic acid (11-11)

[0137]

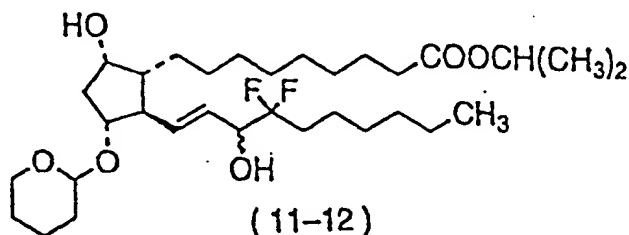


[0138] The compound (11-10) (0.47g) was dissolved in ethanol (8ml), and 1N sodium hydroxide solution (7.7ml) was added to the solution. The mixture was agitated overnight at room temperature. The titled compound (11-11) was obtained by the conventional treatment of the reaction mixture.

11-11)

Isopropyl 9-[2(R)-[4,4-difluoro-3(RS)-hydroxydece-1-nyl]-5(R)-hydroxy-3(R)-(tetrahydropyranyloxy)cyclopentyl] nonanoate (11-12)

[0139]

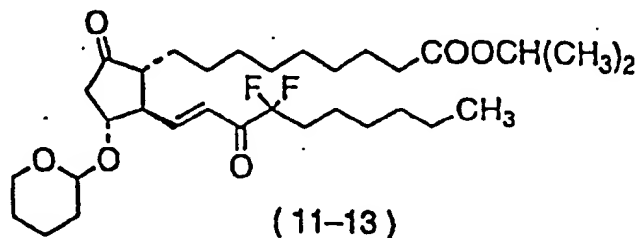


[0140] The compound (11-11) in acetonitrile (6ml) was converted into isopropyl ester with DBU (0.35ml) and isopropyl iodide (0.23ml) at 50°C. The crude product obtained by the conventional treatment of the reaction mixture was purified by silica gel chromatography (n-hexane/ethyl acetate=65/35-55/45) to give the titled compound (11-12) [yield:0.34g (76%;2 reaction processes)].

11-12)

Isopropyl 9-[2(R)-[4,4-difluoro-3-oxodece-1-nyl]-5-oxo-3(R)-(tetrahydropyranyloxy)cyclopentyl]nonanoate (11-13)

[0141]

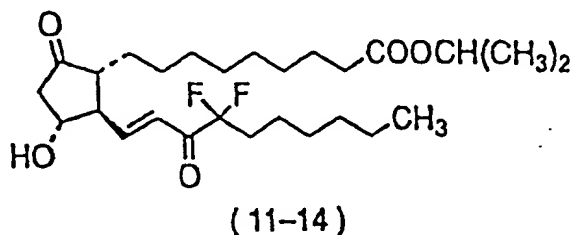


[0142] The compound (11-12) (0.34g) in dichloromethane (8ml) was subjected to Swan oxidation at -78°C with oxalyl chloridé [2M(CH₂Cl₂ solution);1.47ml], DMSO(0.42ml) and triethylamine (3.3ml). The crude product was purified by silica gel chromatography (n-hexane/ethyl acetate=85/15-75/25) to give the titled compound (11-13) [yield:0.24g(71%)].

11-13)

Isopropyl 9-[2(R)-(4,4-difluoro-3-oxodece-1-nyl]-3(R)-hydroxy-5-oxocyclopentyl]nonanoate (11-14)

[0143]



[0144] The compound (11-13) (0.24g) was dissolved in the solvent mixture [acetic acid:water:THF(4:2:1)] (10ml), and the solution was maintained at 40°C for 3.5 hours. The crude product obtained by the conventional treatment of the reaction mixture was purified by silica gel chromatography (n-hexane/ethyl acetate=7/3) to give the titled compound (11-14) [yield:0.17g(82%)].

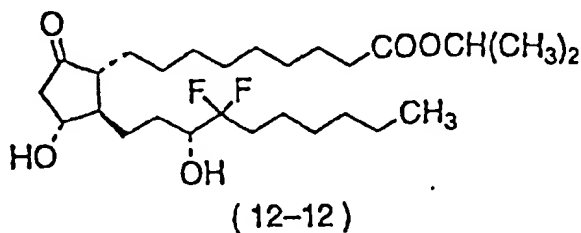
Compound (11-14)

[0145] N.m.r.(CDCl₃)δ : 0.89(3H, t, J = 7.1Hz), 1.21(6 H, d, J=6.5Hz), 1.22-2.90(31H,m), 4.27(1H, q, J = 7.6Hz), 5.00 (1H, sept. J = 6.5Hz), 6.73(1H, d, J=15Hz), 7.12(1H, dd, J = 15Hz, J = 8.6Hz) Mass. m/z 422(M⁺), 404(M⁺-H₂O)

Synthesis example 12

Preparation of isopropyl 9-[2(R)-[4,4-difluoro-3(R)-hydroxydeacyl]-3(R)-(hydroxy-5-oxocyclopentyl)] nonanoate(12-12); [2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-16,16-difluoro-20-ethyl-PGE₁ isopropyl ester (12-12)

[0146]



12-1)

(1S,5R,6R,7R)-6-(4,4-difluoro-3-oxodece-1-nyl)-7-(tetrahydropyranyloxy)-2-oxabicyclo[3.3.0]octan-3-one (12-3)

5 [0147]

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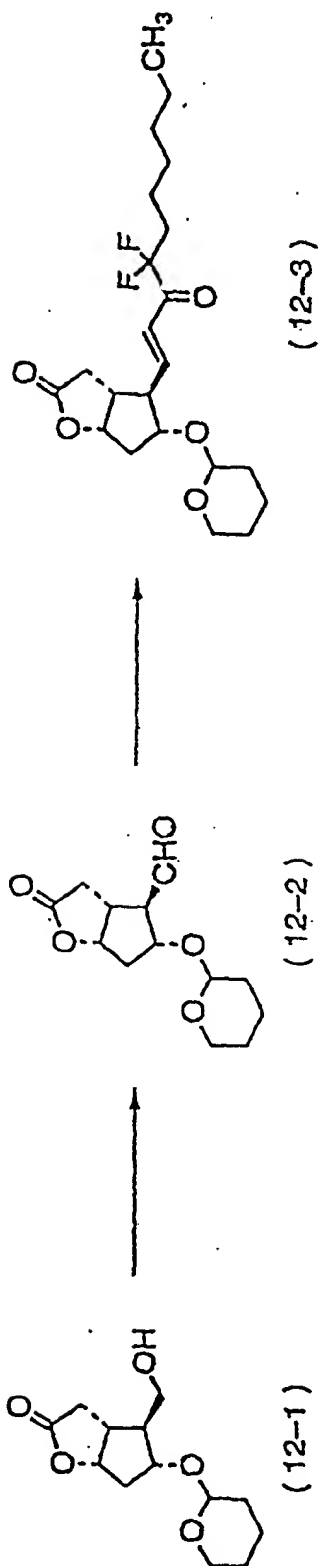
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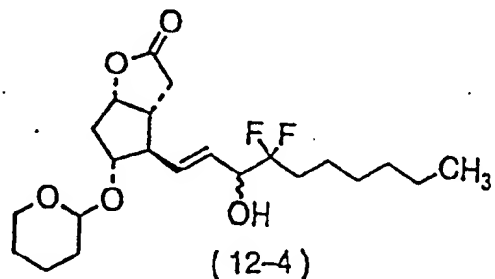
[0148] Corey lactone (12-1) (7.10g) in dichloromethane (200ml) was subjected to Swan oxidation at -78°C with oxalyl chloride [2.0M(CH₂Cl₂ solution);30ml], DMSO (8.45ml) and triethylamine (16.9ml). By the conventional treatment of the reaction mixture, (1S,5R,6R,7R)-6-formyl-7-(4,4-difluoro-3-oxodecyl)-7-(tetrahydropyranyloxy)-2-oxabicyclo

[3.3.0]octane-3-one (12-2) (Corey aldehyde (12-2)) was obtained. The solution of dimethyl (3,3-difluoro-2-oxononyl) phosphonate (7.93g) in THF (10ml) was added to the suspension of sodium hydride (60%;1.11g) in THF (10ml), and the mixture was agitated for 15 minutes, and then zinc chloride (3.77g) was added to the mixture. After adding the solution of Corey aldehyde (12-2) in THF (15ml), the resultant mixture was agitated. The crude product obtained by the conventional treatment of the reaction mixture was purified by silica gel chromatography (n-hexane/ethyl acetate=65/35) to obtain the titled compound (12-3) [yield:5.75g(50%)].

12-2)

(1S,5R,6R,7R)-6-[4,4-difluoro-3(RS)-hydroxydece-1-nyl]-7-(tetrahydropyranyloxy)-2-oxabicyclo[3.3.0]octa-3-one (12-4)

[0149]

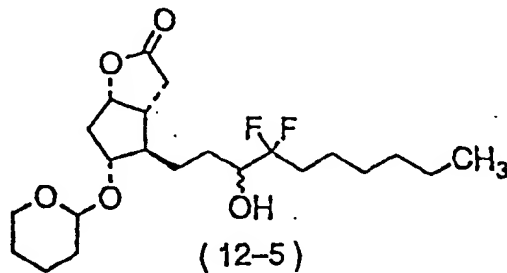


[0150] The solution of the compound (12-3) (4.15g) in THF (30ml) was added to zinc borohydride prepared by the reaction of sodium borohydride (3.03g) and zinc chloride (5.45g) in ether (20ml) to reduce said compound. The crude product obtained by the conventional treatment of the reaction mixture was purified by silica gel chromatography (n-hexane/ethyl acetate=50/50) to give the titled compound (12-4) [yield:3.88g(93%)].

12-3)

(1S,5R,6R,7R)-6-[4,4-difluoro-3(RS)-hydroxydecyl]-7-(tetrahydropyranyloxy)-2-oxabicyclo[3.3.0]octa-3-one (12-5)

[0151]

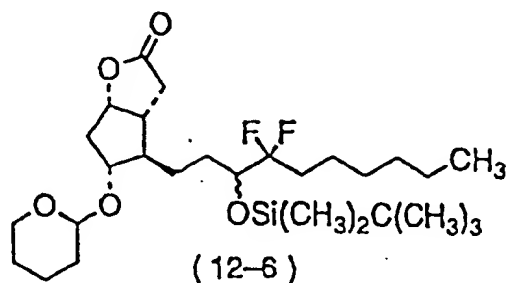


[0152] The compound (12-4) (2.50g) in ethyl acetate (30ml) was subjected to catalytic reduction with 5% Pd-C (0.25g) under H₂ atmosphere. The product was purified by silica gel chromatography (n-hexane/ethyl acetate=1/1) to give the titled compound (12-5) [yield:2.16g(86%)].

12-4)

(1S,5R,6R,7R)-6-[3(RS)-(t-butylidimethylsiloxy)-4,4-difluorodecyl]-7-(tetrahydropyranyloxy)-2-oxabicyclo[3.3.0]octa-3-one (12-6)

[0153]



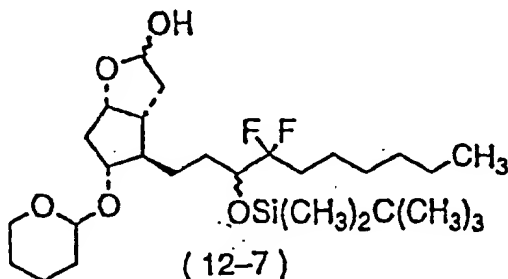
[0154] The compound (12-5) (0.76g) in DMF (4ml) was agitated at 50°C for 15 hours in the presence of imidazole (0.31g) and t-butylidimethylsilane chloride (0.33g). The crude product obtained by the conventional treatment of the reaction mixture was purified by silica gel chromatography (n-hexane/ethyl acetate=7/3) to give the titled compound (12-6) [yield:0.81g(83%)].

[0155] The compound (12-6) was obtained by the same manner as described above by treating the compound (12-5) (1.05g) in DMF (7ml) with imidazole (0.43g) and t-butylidimethylsilane chloride (0.45g) [yield:1.07g(80%)].

12-5)

[1S,3(RS),5R,6R,7R]-6-[3(RS)-(t-butylidimethylsiloxy)-4,4-difluorodecyl]-7-(tetrahydropyranyloxy)-2-oxabicyclo[3.3.0]octa-3-ol (12-7)

[0156]

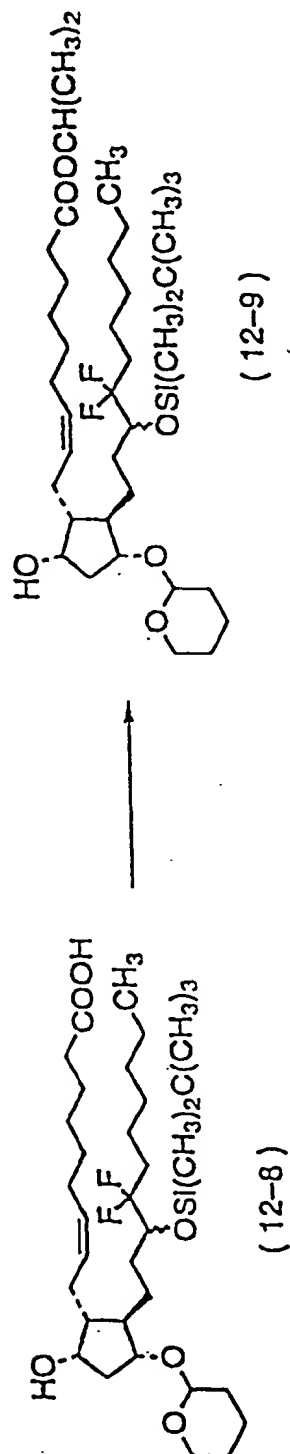


[0157] The compound (12-6) (1.46g) in toluene (7ml) was reduced at -78°C with diisobutylaluminium hydride (DIBAL-H) [1.0M (toluene solution);8.2ml]. The lactol (12-7) was obtained by the conventional treatment of the reaction mixture [yield:1.47g(100%)].

12-6)

isopropyl 9(Z)-{2(R)-[3(RS)-(t-butyldimethylsiloxy)-4,4-difluorodecyl]-5(R)-hydroxy-3(R)-(tetrahydropyranyloxy)
cyclopentyl}non-7-enoate (12-9)

[0158]



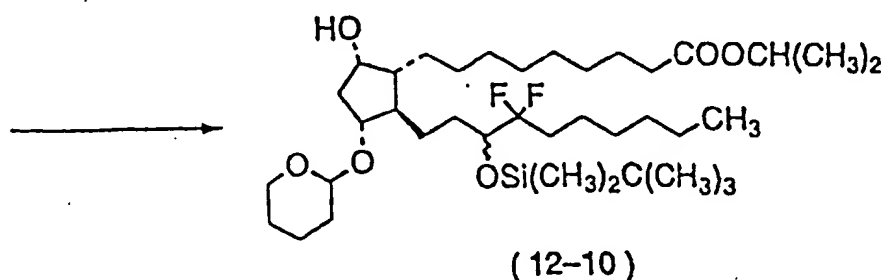
[0159] Potassium t-butoxide [1.0M(THF solution);16.4ml) was added to the suspension of (6-carboxyhexyl) triphenylphosphonium bromide (3.87g) in THF (7ml), and the mixture was agitated for 30 minutes at room temperature. After cooling to -15°C, the solution of lactol (12-7) (1.47g) in THF (7ml) was added to the mixture, and the resultant mixture was warmed slowly to room temperature and left overnight. By the conventional treatment of the reaction mixture, 9 (Z)-{2(R)-[3(RS)-(t-butyl dimethylsiloxy)-4,4-difluorodecyl]-5(R)-hydroxy-3(R)-tetrahydropyranyloxy)cyclopentyl} non-7-enoic acid (12-8) was obtained (yield:3.15g).

[0160] The crude carboxylic acid (12-8) was dissolved in acetonitrile (10ml), and isopropyl iodide (1.09ml) and DBU (1.63ml) were added to the solution. The mixture was held overnight at 40°C. The crude product obtained by the conventional treatment of the reaction mixture was purified by silica gel chromatography (n-hexane/ethyl acetate=8/2) to give the titled compound (12-9) [yield:1.39g (74%;3 reaction processes)].

12-7)

Isopropyl 9-{2(R)-[3(RS)-(t-butyl dimethylsiloxy)-4,4-difluorodecyl]-5(R)-hydroxy-3(R)-(tetrahydropyranyloxy) cyclopentyl}nonanoate (12-10)

[0161]



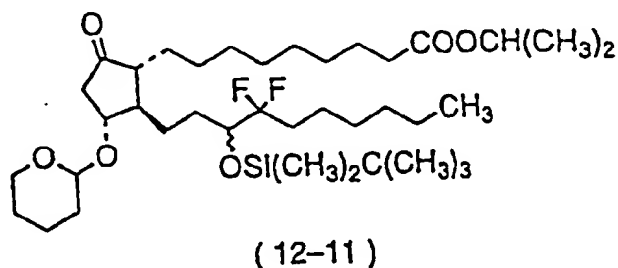
[0162] The compound (12-9)(1.39g) was subjected to catalytic reduction in ethyl acetate (15ml) using 5% Pd-C (0.14g) under hydrogen atmosphere. The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 8/2) to give the titled compound (12-10).

[0163] Yield:1.09g(78%)

12-8)

Isopropyl 9-{2(R)-[3(RS)-(t-butyl dimethylsiloxy)-4,4-difluorodecyl]-5-oxo-3(R)-(tetrahydropyranyloxy)cyclopentyl} nonanoate (12-11)

[0164]



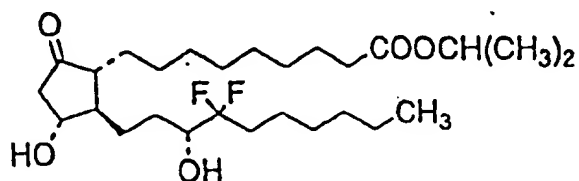
[0165] A solution of the compound (12-10)(1.09g) in dichloromethane (2ml) was subjected to Swann oxydation using oxalyl chloride(2.0M, CH₂Cl₂ solution, 1.58ml), a solution of DMSO (0.45ml) in dichloromethane (10ml) and triethylamine (0.88ml). The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 8/2) to give the titled compound (12-11).

[0166] Yield:0.93g(86%)

12-9)

Isopropyl 9-[2(R)-[4,4-difluoro-3(R)-hydroxydecyl]-3(R)-hydroxy-5-oxocyclopentyl]nonanoate (12-12)

[0167]



(12-12)

[0168] The compound (12-11)(0.93g) was hydrolyzed in acetonitrile (30ml) with 46% hydrofluoric acid(1.55ml). The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 7/3-1/1), and the compound obtained was further fractionated by HPLC to give isopropyl 9-[2(R)-[4,4-difluoro-3(R)-hydroxydecyl]-3(R)-hydroxy-5-oxocyclopentyl]nonanoate (12-12).

[0169] Yield:0.16g(24%)

[0170] N.m.r.(CDCl₃) δ:0.89(3H,t,J=7.0Hz), 1.22(6H,d,J=6.5Hz), 1.24 -2.80(36H,m), 3.73(1H,m), 4.16(1H,q, J=6.5Hz), 5.00 (1H,Sept,J=6.5Hz)

[0171] Mass. m/z:490(M⁺),472(M⁺-H₂O)

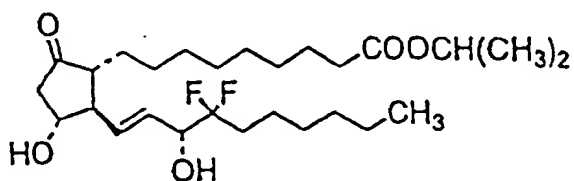
[0172] Rf.value: 0.50 (silica gel 60, n-hexane/ethyl acetate = 3/7);

[0173] And 0.15g of 17β-isomer was obtained.

Synthesis Example 13

Preparation of isopropyl 9-[2(R)-[4,4-difluoro-3(R)-hydroxydece-1-nyl]-3(R)-hydroxy-5-oxocyclopentyl]nonanoate (13-12); [2-decarboxy -2-(2-carboxyethyl)-16,16-difluoro-20-ethyl-PGE₁ isopropyl ester] (13-12)

[0174]



(13-12)

13-1)

Isopropyl 9-[2(R)-(t-butyl dimethylsiloxy methyl)-5(R)-hydroxy-(3R)-(tetrahydropyranyloxy)cyclopentyl]nonanoate
(13-2)

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[0175]

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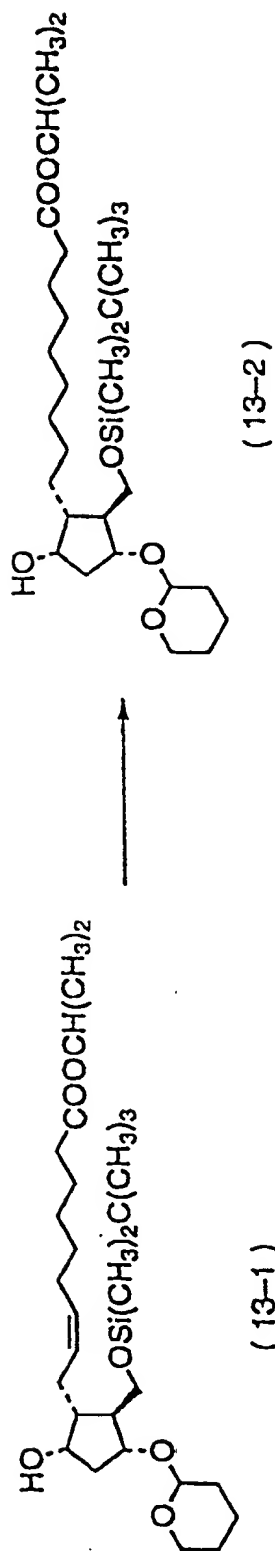
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[0176] The compound (13-1)(5.89g) obtained according to the same way as in Experiments (1-1) - (1-3) of Example 1 was subjected to catalytic reduction in ethyl acetate (80ml) with 5% Pd-C (0.6g) and hydrogen gas. The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 8/2) to

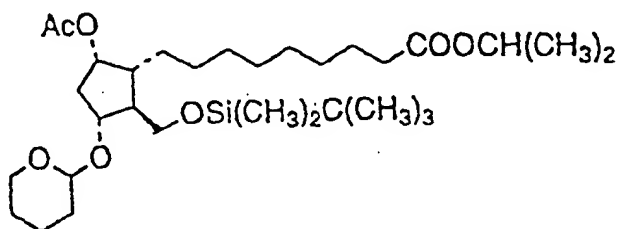
give the titled compound (13-2).

[0177] Yield: 3.93g (66%)

13-2)

Isopropyl 9-[5(R)-(acetoxymethyl)-2(R)-(tert-butyldimethylsilyloxymethyl)-3(R)-(tetrahydropyranyloxy)cyclopentyl]nonanoate (13-3)

[0178]



(13-3)

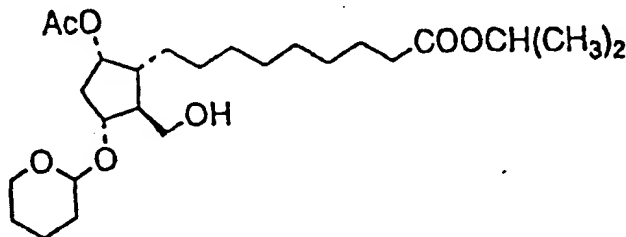
[0179] The compound (13-2) (3.93g) was acetylated in dichloromethane (40ml) at room temperature using pyridine (1.80ml) and acetyl chloride (1.59ml). The titled compound (13-3) was obtained by the conventional treatment.

[0180] Yield: 4.05g (95%)

13-3)

Isopropyl 9-[5(R)-(acetoxymethyl)-2(R)-(hydroxymethyl)-3(R)-(tetrahydropyranyloxy)cyclopentyl]nonanoate (13-4)

[0181]



(13-4)

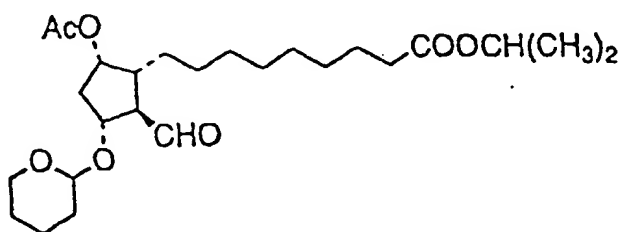
[0182] To the solution of the compound (13-3) (4.05g) in THF (8ml), tetrabutylammonium fluoride (1M, THF solution, 8.51ml) was added at room temperature and the mixture was left overnight. The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 6/4) to give the titled compound (13-4).

[0183] Yield: 3.18g (98%)

13-4)

Isopropyl 9-[5(R)-(acetoxo)-2(R)-formyl-3(R)-(tetrahydropyranyloxy) cyclopentyl]nonanoate (13-5)

[0184]



(13-5)

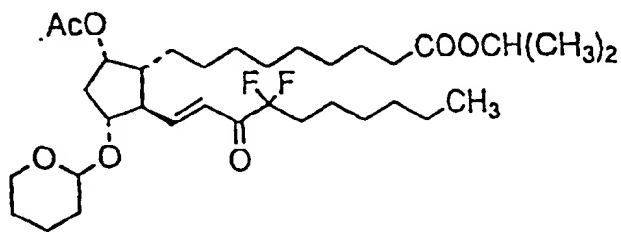
[0185] A solution (10ml) of the compound (13-4) (3.18g) in dichloromethane was subjected to Swan oxydation using oxalyl chloride (2M, CH_2Cl_2 solution, 8.78ml), a solution (20ml) of DMSO (2.49 ml) in dichloromethane and triethylamine (5.87ml). The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 7/3) to give the titled compound (13-5).

[0186] Yield: 3.10g (98%)

13-5)

Isopropyl 9-[5(R)-(acetoxo)-2(R)-(4,4-difluoro-3-oxodece-1-nyl)-3(R)-(tetrahydropyranyloxy)cyclopentyl]nonanoate (13-6)

[0187]



(13-6)

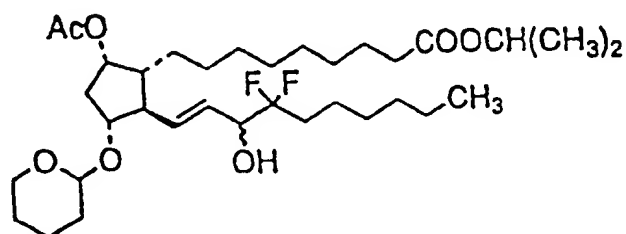
[0188] To dimethyl(3,3-difluoro-2-oxononyl)phosphonate anion prepared from sodium hydride (60%, 0.83g) suspended in THF (20ml) and dimethyl(3,3-difluoro-2-oxononyl)phosphonate (5.95g), a solution (20ml) of the aldehyde (13-5) (3.10g) in THF was added and refluxed as heating for 70 hours. The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 85/15) to give the titled compound (13-6).

[0189] Yield: 2.96g (71%)

13-6)

Isopropyl 9-[5(R)-(acetoxo)-2(R)-[4,4-difluoro-3(RS)-hydroxydece-1-nyl]-3(R)-(tetrahydropyranyloxy)cyclopentyl] nonanoate (13-7)

[0190]



(13-7)

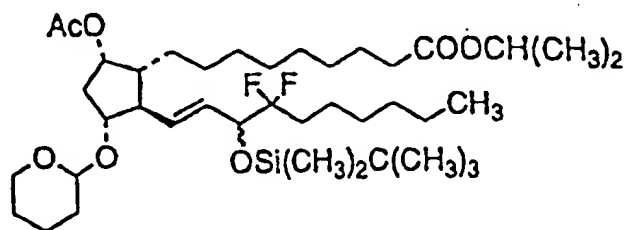
[0191] To zinc borohydride prepared from sodium borohydride (1.09g) and zinc chloride (1.97g), a solution (10ml) of α,β -unsaturated ketone (13-6)(2.96g) in THF was added in ether (40ml) and the mixture was stirred for 1 hour at 0 °C. The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 8/2) to give the titled compound (13-7).

[0192] Yield: 2.62g (89%)

13-7)

Isopropyl 9-[5(R)-(acetoxo)-2(R)-[4,4-difluoro-3(RS)-(t-butyldimethylsiloxy)dece-1-nyl]-3(R)-(tetrahydropyranyloxy)cyclopentyl] nonanoate (13-8)

[0193]



(13-8)

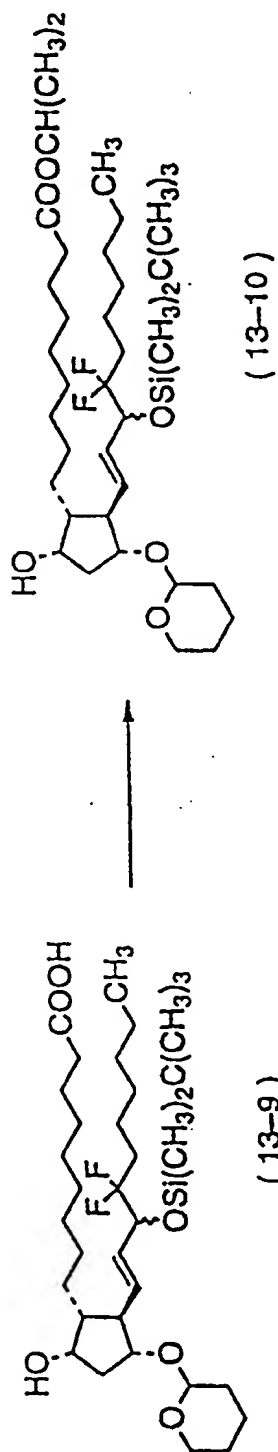
[0194] The compound (13-7)(2.62g) was dissolved in DMF (16ml) and to resultant solution, imidazol (2.89g) and t-butyldimethylsilane chloride (3.20g) were added. The mixture was stirred over three days. The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 85/15) to give the titled compound (13-8).

[0195] Yield: 3.11g (100%)

13-8)

Isopropyl 9-[5(R)-[4,4-difluoro-3(RS)-(t-butylidimethylsiloxy)dece-1-nyl]-3(R)-(tetrahydropyranyloxy)cyclopentyl]nonanoate (13-10)

[0196]



[0197] The compound (13-8)(3.11g) was dissolved in ethanol (43ml) and to this solution, 1N-sodium hydroxide aque-

ous solution (42.5g) was added, and resultant mixture was stirred for 34 hours at room temperature. Using conventional treatment, 9-[2(R)-[4,4-difluoro-3(RS)-(t-butyl)dimethylsiloxy]dece-1-nyl]-5(R)-hydroxy-3(R)-(tetrahydropyranyloxy)cyclopentyl] nonanoic acid (13-9) was obtained.

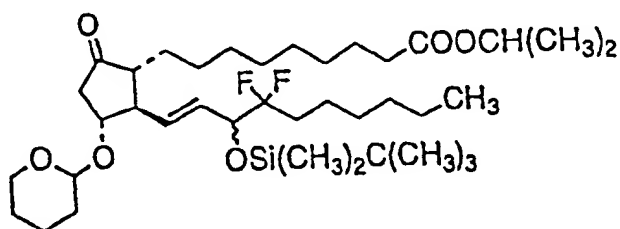
[0198] The carboxylic acid (13-9) was dissolved in acetonitrile (16ml) and to this solution, isopropyl iodide (1.69ml) and DBU (2.54ml) were added, and the mixture was stirred for 2 hours at 50 - 55 °C. The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 8/2) to give the titled compound (13-10).

[0199] Yield: 2.60g (89%, 2 reaction processes)

13-9)

Isopropyl 9-[2(R)-[4,4-difluoro-3(RS)-(t-butyl)dimethylsiloxy]dece-1-nyl]-3(R)-(tetrahydropyranyloxy)-5-oxocyclopentyl]nonanoate (13-11)

[0200]



(13-11)

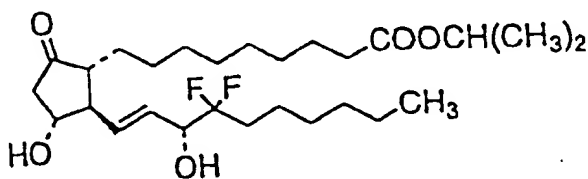
[0201] Oxalyl chloride (2M, in CH₂Cl₂, 2.28ml) was diluted by dichloromethane (15ml) and the solution was cooled to -78°C, to which the solution, DMSO (0.65ml) was added and the mixture was stirred for 30 minutes. To this mixture, a solution (10ml) of the compound (15-10) (1.57g) in dichloromethane and then triethylamine (1.58ml) were added, in which the mixture was subjected to Swan oxydation. The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 85/15) to give the titled compound (13-11).

[0202] Yield: 1.53g (98%)

13-10)

Isopropyl 9-[2(R)-[4,4-difluoro-3(R)-hydroxydece-1-nyl]-3(R)-hydroxy-5-oxocyclopentyl]nonanoate (13-12)

[0203]



(13-12)

[0204] The compound (13-11) (0.28g) was dissolved in acetonitrile (5.5ml) and into this solution, 47% hydrofluoric acid was added, stirred for 3 hours at 0 °C and for 5 hours at room temperature. The crude product obtained by the conventional treatment was purified by silica gel chromatography (n-hexane/ethyl acetate = 7/3 - 1/1) to give the titled compound (13-12).

[0205] Yield: 0.061g (31%)

[0206] N.m.r. (CDCl₃) δ: 0.88(3H, t, J=7.6Hz), 1.22(6H, d, J=6.6Hz), 1.25-2.85(30H, m), 3.48(2H, br), 4.07(1H, q, J=7.5Hz), 4.26(1H, m), 4.99(1H, sept, J=6.6Hz), 5.78(2H, m).

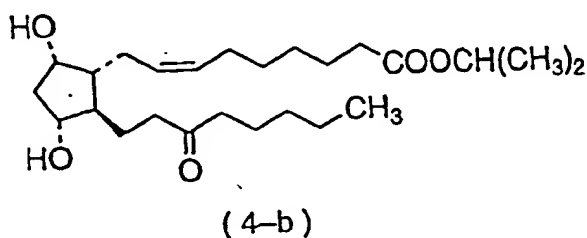
[0207] Mass. m/z: 470(M⁺-H₂O), 451(M⁺-H₂O-F)

[0208] Rf.value: 0.35(silica gel 60, n-hexane/ethyl acetate = 3/7)

[0209] Further, 0.071g(36%) of 17 β-isomer was obtained.

Synthesis Example 14

[0210] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-PGF_{2α} isopropyl ester [IUPAC name: isopropyl (Z)-9-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxooctyl)cyclopentyl]-7-nonenoate] (4-b)



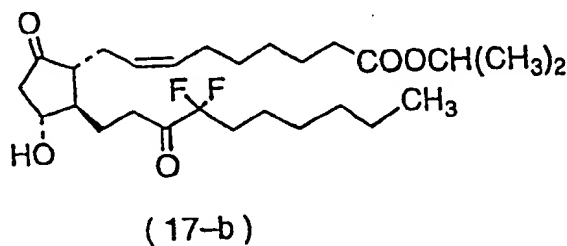
[0211] Except for using the compound(3-b) (P₁=tetrahydropyranyl, P₂=-CH₂-CH₂-, X₁=X₂=H, R₂-R₃=butyl, P₃=isopropyl), the titled compound (4-b) was obtained by the same way as Synthesis Example 1.

The compound(4-b)(in the compound (4), X₁=X₂=H, R₂-R₃=butyl, P₃=isopropyl)

[0212] N.M.R.(CDCl₃) δ:0.88(3H,t,J=7.5Hz), 1.23(6H,d,J=6.0Hz), 1.23-2.50(28H,m), 2.26(2H,t,J=7.5Hz), 2.42(2H,t,J=7.5Hz), 2.58(2H,t,J=7.5Hz), 2.85(1H,br,d), 3.88(1H,br), 4.17(1H,br), 5.00(1H,Sept,J=6.0Hz), 5.41(2H,m).

Synthesis Example 15

[0213] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE₂ isopropyl ester [IUPAC name: isopropyl (Z)-9-[(1R,2R,3R)-2-(4,4-difluoro-3-oxodecyl)-3-hydroxy-5-oxocyclopentyl]-7-nonenoate] (17-b)



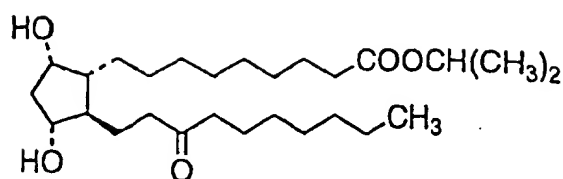
[0214] Except for using dimethyl(3,3-difluoro-2-oxononyl) phosphonate, the titled compound (17-b) was obtained by the same way as Synthesis Example 3.

Compound (17-b)(in compound (17), X₁=X₂=F, R₂-R₃=hexyl, isopropyl ester)

[0215] N.M.R.(CDCl₃) δ:0.91(3H,t,J=7.5Hz), 1.24(6H,d,J=6.0Hz), 1.24-2.50(26H,m), 2.26(1H,dd,J=17.5Hz, J=10.0Hz), 2.28(2H,t, J=7.5Hz), 2.62(1H,dd,J=17.5Hz, J=6.5Hz), 2.78(1H,br,s), 4.22(1H, m), 5.02(1H,Sept,J=6.0Hz), 5.39(2H,m).

Synthesis Example 16

[0216] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-20-ethyl-PGF_{1α} isopropyl ester [IUPAC name: isopropyl 9-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-nonanoate] (16-1)



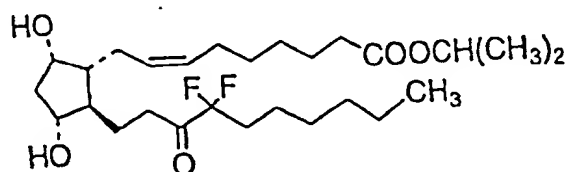
(16-1)

[0217] The compound (4-a) of Synthesis Example 1 was subjected to hydrogenation using 5%Pd-C and hydrogen gas in ethyl acetate and the resultant was purified on silica gel column to obtain the titled compound (16-1).

[0218] N.M.R.(CDCl₃) δ:0.89(3H,t,J=7.5Hz), 1.23(6H,d,J=6.0Hz), 1.27-2.03(29H,m), 1.18(2H,br,s), 2.26(2H,t,J=7.5Hz), 2.41(2H,t, J=7.5Hz), 2.56(2H,br,t,J=6.5Hz), 2.66(2H,br,s), 3.91(1H,br,s), 4.20(1H,br,s), 5.00(1H,Sept,J=6.0Hz).

Synthesis Example 17

[0219] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGF_{2α} isopropyl ester [IUPAC name: isopropyl Z-9-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(4,4-difluoro-3-oxodecyl)cyclopentyl]-7-nonenoate] (32-b)



(32-b)

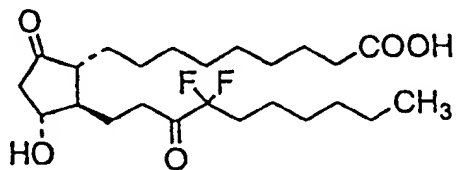
[0220] Except for using the compound (12-b)(X₁=X₂=F, P₁=tetrahydropyranyl, R₂-R₃=hexyl in compound (12)) and isopropyl iodide for esterification, titled Compound (32-b) was obtained in the same way as Synthesis Example 7.

[0221] The compound (32-b)(X₁=X₂=F, R₂-R₃=hexyl, P₃=isopropyl in the compound (32))

[0222] N.M.R.(CDCl₃) δ:0.89(3H,t,J=5Hz), 1.24(6H,d,J=6.0Hz), 1.24-2.37(28H,m), 2.26(2H,t,J=7.0Hz), 2.47(1H,dt,J=12.5Hz,J=7.5Hz), 2.71(0.7H,m), 2.83(0.3H,m), 3.70(0.7H,m), 3.90(0.3H,br,s), 4.26(1H,br,s), 5.00(1H,Sept,J=6.0Hz), 5.43(2H,m).

Synthesis Example 18

[0223] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE₁ [IUPAC name: 9-[(1R,2R,3R)-3-hydroxy-5-oxo-2-(4,4-difluoro-3-oxodecyl) cyclopentyl]-nonanoic acid] (33-b)



(33-b)

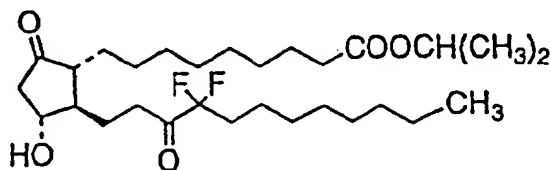
[0224] The titled compound (33-b) was obtained in the same way as Synthesis Example 8, except for using Compound (14-b)(X₁=X₂=F, P₁=tetrahydropyranyl, R₂-R₃=hexyl in the compound (14)).

[0225] Compound (33-b)(X₁=X₂=F, R₂-R₃=hexyl in Compound (33)).

[0226] N.M.R.(CDCl₃) δ :0.90(3H,t,J=7.5Hz), 1.06-1.14(38H,m), 2.25(1H,dd,J=17.5Hz,J=11.5Hz), 2.35(2H,t,J=7.5Hz), 2.59(1H,dd, J=17.5Hz,J=7.5Hz), 4.19(1H,m).

Synthesis Example 19

[0227] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-butyl-PGE₁ isopropyl ester [IUPAC name: isopropyl 9-[(1S,2S,3S)-3-hydroxy-5-oxo-2-(4,4-difluoro-3-oxododecyl)cyclopentyl]-nonanoate] (20-c)



(20-c)

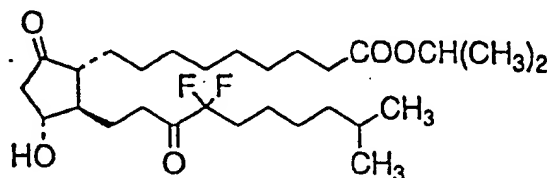
[0228] The titled compound (20-c) was obtained in the same way as Synthesis Example 4, except for using the compound (15-d)(X₁=X₂=F, P₁=tetrahydropyranyl, R₂-R₃=octyl P₃=isopropyl in the compound (15)).

[0229] The compound (20-c)(X₁=X₂=F, R₂-R₃=octyl, P₃=isopropyl in the compound (20)).

[0230] N.M.R.(CDCl₃) δ :0.89(3H,t,J=7.5Hz), 1.23(6H,d,J=6.0Hz), 1.23-2.15(34H,m), 2.24(1H,dd,J=17.5Hz,J=10.0Hz), 2.26(2H,t, J=7.5Hz), 2.58(1H,dd,J=17.5Hz,J=6.5Hz), 2.88(1H,br,s), 4.18(1H,m), 5.00(1H,Sept,J=6.0Hz).

Synthesis Example 20

[0231] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-isopropyl-PGE₁ isopropyl ester [IUPAC name: isopropyl 9-[(1R,2R,3R)-3-hydroxy-5-oxo-2-(4,4-difluoro-9-methyl-3-oxodecyl)cyclopentyl]-nonanoate] (20-d)



(20-d)

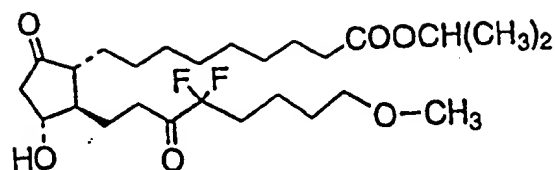
[0232] The titled compound (20-d) was obtained in the same way as Synthesis Example 4, except for using Compound (15-d)(X₁=X₂=F, P₁=tetrahydropyranyl, R₂-R₃=1-methylhexyl, P₃=isopropyl in the compound (15)).

[0233] Compound (20-d)(X₁=X₂=F, R₂-R₃=1-methylhexyl, P₃=isopropyl in the compound (20)).

[0234] N.M.R.(CDCl₃) δ :0.87(6H,d,J=7.0Hz), 1.22(6H,d,J=6.0Hz), 1.22-2.12(29H,m), 2.23(1H,dd,J=12.5Hz,J=10.0Hz), 2.24(2H,t,J=7.5Hz), 2.56(1H,dd,J=17.5Hz,J=7.5Hz), 2.97(1H,br,s), 4.17(1H,m), 4.99(1H,Sept,J=6.0Hz).

Synthesis Example 21

[0235] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-methoxy-PGE₁ isopropyl ester [IUPAC name: isopropyl 9-[(1R,2R,3R)-3-hydroxy-5-oxo-2-(4,4-difluoro-8-methoxy-3-oxooctyl)cyclopentyl]-nonanoate] (20-e)



(20-e)

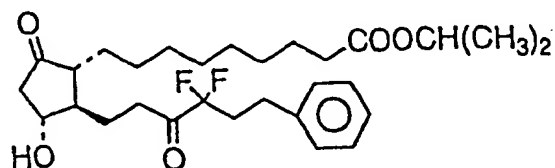
[0236] The titled compound (20-e) was obtained in the same way as Synthesis Example 4, except for using Compound (15-e) ($X_1=X_2=F$, P_1 =tetrahydropyranyl, R_2-R_3 =methoxybutyl, P_3 =isopropyl in the compound (15)).

[0237] The compound (20-e) ($X_1=X_2=F$, R_2-R_3 =methoxybutyl, P_3 =isopropyl in the compound (20)).

[0238] N.M.R.(CDCl₃) δ : 1.23(6H,d,J=6.0Hz), 1.23-2.15(27H,m), 2.23(1H,dd,J=17.5Hz,J=11.5Hz), 2.24(2H,t,J=7.5Hz), 2.57(1H,dd,J=17.5Hz,J=7.5Hz), 2.98(1H,br,s), 3.34(3H,s), 3.40(2H,m), 4.18(1H,m), 5.00(1H,Sept,J=6.0Hz).

Synthesis Example 22

[0239] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-19,20-bisnor-18-phenyl-PGE₁ isopropyl ester [IUPAC name: isopropyl 9-[(1R,2R,3R)-3-hydroxy-5-oxo-2-(4,4-difluoro-6-phenyl-3-oxohexyl)cyclopentyl]-nonanoate] (20-f)



(20-f)

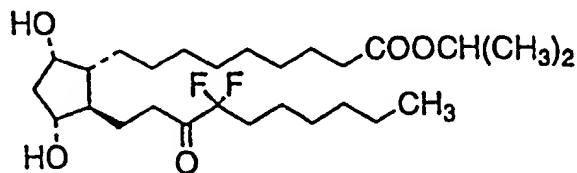
[0240] The titled compound (20-f) was obtained in the same way as Synthesis Example 4, except for using Compound (15-f) ($X_1=X_2=F$, P_1 =tetrahydropyranyl, R_2-R_3 =phenylethyl, P_3 =isopropyl in the compound (15)).

[0241] Compound (20-f) ($X_1=X_2=F$, R_2-R_3 =phenylethyl, P_3 =isopropyl in the compound (20)).

[0242] N.M.R.(CDCl₃) δ : 1.22(6H,d,J=6.0Hz), 1.22-2.55(22H,m), 2.22 (1H,dd,J=16.5Hz,J=12.5Hz), 2.24(2H,t,J=7.5Hz), 2.55(1H,dd, J=17.5Hz,J=7.5Hz), 2.88(2H,t,J=7.5Hz), 3.17(1H,br,s), 4.17(1H,m), 4.99(1H,Sept,J=6.0Hz), 7.25(5H,m).

Synthesis Example 23

[0243] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGF_{1 α} isopropyl ester [IUPAC name: isopropyl 9-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(4,4-difluoro-3-oxodecyl)cyclopentyl]-nonanoate] (23-1)



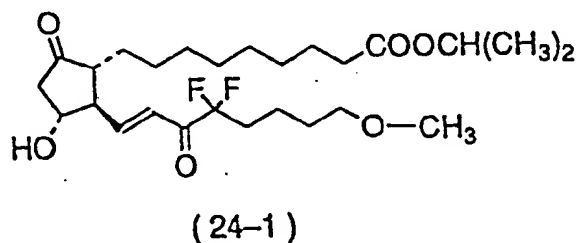
(23-1)

[0244] The compound (32-b) of Synthesis Example 17 was subjected to hydrogenation using 5%Pd-C and hydrogen gas in ethyl acetate and the resultant was purified on silica gel column to give the titled compound (23-1).

[0245] N.M.R.(CDCl₃) δ:0.90(3H,t,J=7.5Hz), 1.23(6H,d,J=6.5Hz), 1.26-2.15(32H,m), 2.26(2H,t,J=7.5Hz), 2.49(1H, dt,J=7.5Hz,J=7.5Hz), 2.66 (8H,br,s), 2.82(0.2H,br,t,J=6.0Hz), 3.70(0.8H,q,J=6.8Hz), 3.92 (0.2H,m), 4.24(1H,m), 5.00 (1H,Sept,J=6.5Hz).

Synthesis Example 24

[0246] The preparation of 2-decarboxy-2-(2-carboxyethyl)-15-keto-16,16-difluoro-20-methoxy-PGE₁ isopropyl ester [IUPAC name: isopropyl 9-[(1R,2R,3R)-3-hydroxy-5-oxo-2-(E-4,4-difluoro-8-methoxy-3-oxooct-1-enyl)cyclopentyl]-nonanoate] (24-1)

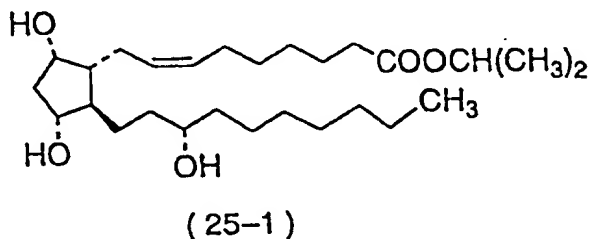


[0247] The titled compound (24-1) was obtained in the same way as Synthesis Example 11, except that the reaction was performed using the compound (11-8) of Synthesis Example 11 and dimethyl(3,3-difluoro-7-methoxyheptyl)phosphonate.

[0248] N.M.R.(CDCl₃) δ:1.23(6H,d,J=6.0Hz), 1.23-1.44(9H,m), 1.44-1.80(9H,m), 1.90-2.30(3H,m), 2.25(2H,t, J=6.5Hz), 2.32(1H,dd, J=17.5Hz,J=7.5Hz), 2.60-2.72(2H,m), 2.82(1H,dd,J=17.5Hz,J=7.5Hz), 3.33(3H,s), 3.39(2H,t, J=5.0Hz), 4.25(1H,q,J=7.5Hz), 5.00(1H, Sept,J=6.0Hz), 6.73(1H,dd,J=15.0Hz), 7.12(1H,dd,J=15.0Hz,J=7.5Hz).

Synthesis Example 25

[0249] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-20-ethyl-PGF_{2α} isopropyl ester [IUPAC name: isopropyl Z-9-[(1R,2R, 3R,5S)-3,5-dihydroxy-2-(3(S)-hydroxydecyl)cyclopentyl]-7-nonenoate] (25-1)

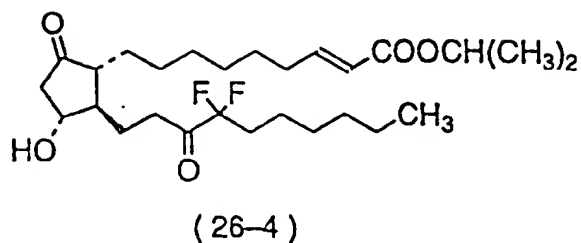


[0250] The compound (28-b)(X₁=X₂=H, P₁=P₆=tetrahydropyranyl, R₂-R₃=hexyl, P₃=isopropyl in the compound (28)) was subjected to deprotection in solvent of acetic acid-water-THF and then the resultant was purified on silica gel column to give the titled compound.

[0251] N.M.R.(CDCl₃) δ:0.90(3H,t,J=7.5Hz), 1.23(6H,d,J=6.0Hz), 1.23-1.80(26H,m), 1.89(2H,t,J=2.5Hz), 2.10(2H, m), 2.20(1H,d, J=5.0Hz), 2.27(2H,t,J=5.0Hz), 2.30(1H,m), 2.62(1H,d,J=7.5Hz), 3.64(1H,m), 3.98(1H,m), 4.20(1H,m), 5.01(1H,Sept,J=6.0Hz), 5.44(2H,m).

Synthesis Example 26

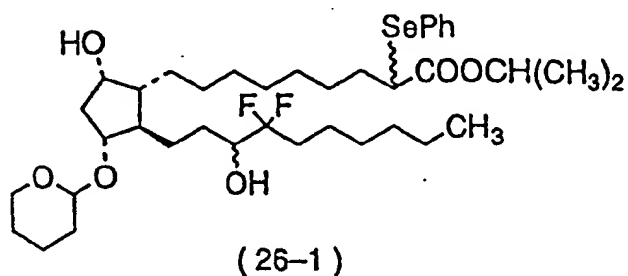
[0252] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-Δ²-PGE₁ isopropyl ester [IUPAC name: isopropyl E-9-[(1R,2R,3R)-3-hydroxy-5-oxo-2-(4,4-difluoro-3-oxodecyl)cyclopentyl]-2-nonenoate] (26-4)



26-1)

Isopropyl 9- [(1R,2R,3R,5S)-3-tetrahydropyranyloxy-5-hydroxy-2-(4,4-difluoro-3(RS)-hydroxydecyl)cyclopentyl]-2 (RS)-phenylselenenyl nonanoate (26-1)

[0253]



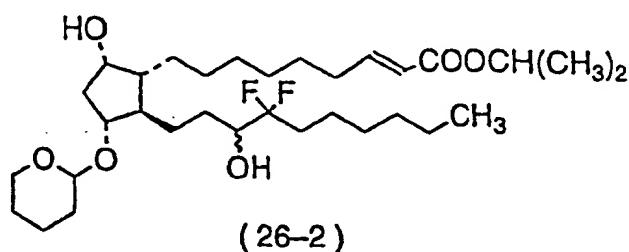
[0254] The compound (18-b) ($X_1=X_2=F$, P_1 =tetrahydropyranyl, R_2-R_3 =hexyl, P_3 =isopropyl in the compound (18)) (0.632g) was reacted using lithium diisopropylamide (LDA) and diphenyldiselenide in THF to give the compound (26-1).

[0255] Yield: 0.518g (65%)

26-2)

Isopropyl E-9-[(1R,2R,3R,5S)-3-tetrahydropyranyloxy-5-hydroxy-2-(4,4-difluoro-3(RS)-hydroxydecyl)cyclopentyl]-2-nonenoate] (26-2)

[0256]



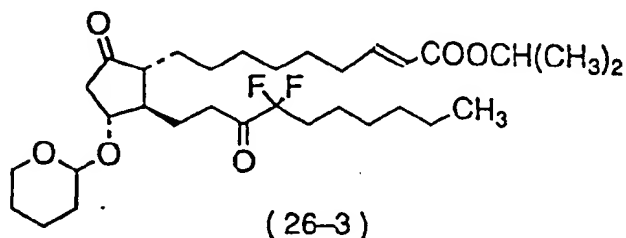
[0257] The compound (26-1) was reacted using 31% hydrogen peroxide in mixture of ethyl acetate-methanol and the resultant was purified on silica gel column to give the compound (26-2).

[0258] Yield: 0.393g (76%).

26-3)

Isopropyl E-9-[(1R,2R,3R)-3-tetrahydropyranyloxy-5-oxo-2-(4,4-difluoro-3-oxodecyl)cyclopentyl]-2-nonenolate] (26-3)

[0259]



[0260] The compound (26-2) was subjected to Swan oxydation and the resultant was purified on silica gel column to give the compound (26-3).

[0261] Yield: 0.318g (81%)

26-4)

Isopropyl E-9-[(1R,2R,3R)-3-hydroxy-5-oxo-2-(4,4-difluoro-3-oxodecyl)cyclopentyl]-2-nonenolate] (26-4)

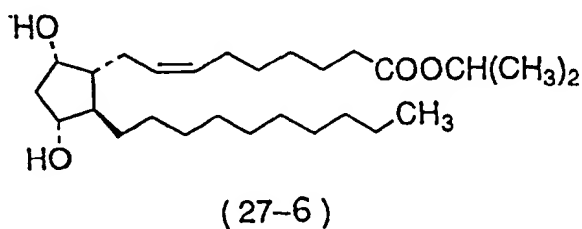
[0262] The compound (26-3) was subjected to deprotection in the mixture of acetic acid-water-THF and then the resultant was purified on silica gel column to give the titled compound (26-4).

[0263] Yield: 0.177g (65%)

[0264] N.M.R. (CDCl₃) δ: 0.90(3H, t, J=7.5Hz), 1.27(6H, d, J=6.0Hz), 1.27-2.10(27H, m), 2.16(1H, t, J=6.5Hz), 2.20(1H, br), 2.24(1H, dd, J=17.5Hz, J=11.0Hz), 2.59(1H, dd, J=17.5Hz, J=7.5Hz), 2.71(1H, br, s), 4.18(1H, m), 5.06(1H, Sept, J=6.0Hz), 5.78(1H, d, J=16.0Hz), 6.94(1H, dt, J=17.5Hz, J=7.0Hz).

Synthesis Example 27

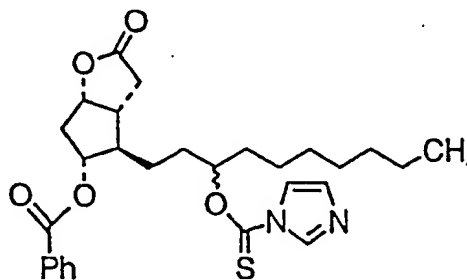
[0265] The preparation of 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-dehydroxy-20-ethyl-PGF_{2α} isopropyl ester [IUPAC name: isopropyl Z-9-[(1R,2R,3R,5S)-3,5-dihydroxy-2-decylcyclopentyl]-7-nonenolate] (27-6)



27-1)

(1S,5R,6R,7R)-7-benzoyloxy-6-[3(RS)-imidazolylthiocarbonyloxydecyl]-2-oxabicyclo[3.3.0]octane-3-one(27-1)

[0266]



(27-1)

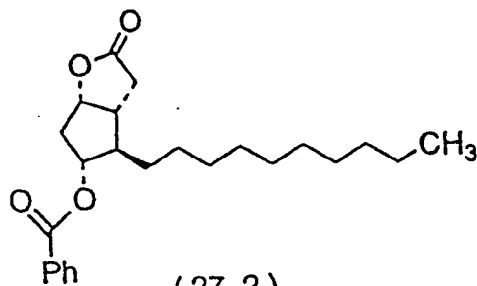
[0267] The compound (12-c)($X_1=X_2=H$, P_1 =phenyl, R_2-R_3 =hexyl, in the compound (12))(0.6768g) was reacted with 1,1'-thiocarbonyl imidazole in 1,2-dichloromethane and the resultant was purified on silica gel column to give the compound (27-1).

[0268] Yield:0.7959g(92.4%)

27-2)

(1S,5R,6R,7R)-7-benzoyloxy-6-decyl-2-oxabicyclo[3.3.0] octane-3-one(27-2)

[0269]



(27-2)

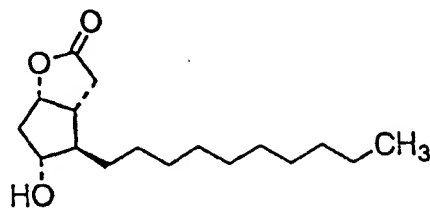
[0270] The compound (27-1) was reacted with tributyltin hydride in toluene and the resultant was purified on silica gel column to give the compound (27-2).

[0271] Yield:0.5688g(94.8%)

27-3)

(1S,5R,6R,7R)-6-decyl-7-hydroxy-2-oxabicyclo[3.3.0]octane-3-one (27-3)

[0272]



(27-3)

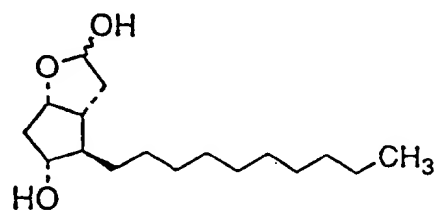
[0273] The compound (27-2) was reacted with potassium carbonate in dry methanol and the resultant was purified on silica gel column to give Compound (27-3).

[0274] Yield: 0.3420g (82.3%)

27-4)

(1S,3(RS),5R,6R,7R)-6-decyl-7-hydroxy-2-oxabicyclo[3.3.0] octane-3-ol(27-4)

[0275]



(27-4)

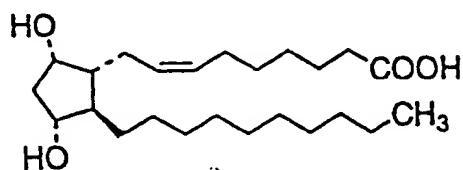
[0276] The compound (27-3) was reacted with DIBAL-H in toluene to give the compound (27-4). Yield: 0.2304g (66.9%). 0.0940g of the compound (27-3) was recovered, which was reacted in the same way to give 0.0947g of the compound (27-4).

[0277] Total yield: 0.3251g.

27-5)

Z-9-[(1R,2R,3R,5S)-3,5-dihydroxy-2-decylcyclopentyl]-7-nonenoic acid(27-5)

[0278]



(27-5)

[0279] The compound (27-4) was reacted with the ylide prepared from the compound (e) of Synthesis Example 1 to give the compound (27-5).

[0280] Yield:0.9246g

27-6)

Isopropyl Z-9-[(1R,2R,3R,5S)-3,5-dihydroxy-2-decylcyclopentyl]-7-nonenoate(27-6)

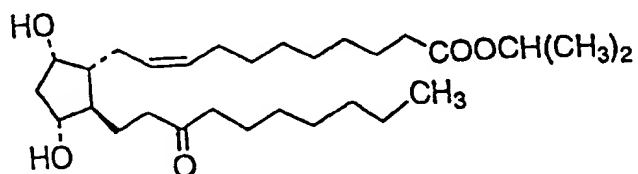
[0281] The compound (27-5) was reacted with isopropyl iodide and DBU in dry acetonitrile and the resultant was purified on silica gel column to give the titled compound (27-6).

[0282] Yield:0.3860g(77.0%)

[0283] N.M.R.(CDCl₃) δ:0.88(3H,t,J=7.5Hz), 1.23(6H,d,J=6.5Hz), 1.25-1.50(23H,m), 1.50-1.75(3H,m), 1.86(2H,m), 2.10(2H,q, J=5.1Hz), 2.27(4H,quint,J=7.5Hz), 2.41(1H,br), 2.67(1H,br), 3.94(1H,br), 4.18(1H,br), 5.00(1H,Sept, J=6.5Hz), 5.42(2H,m).

Synthesis Example 28

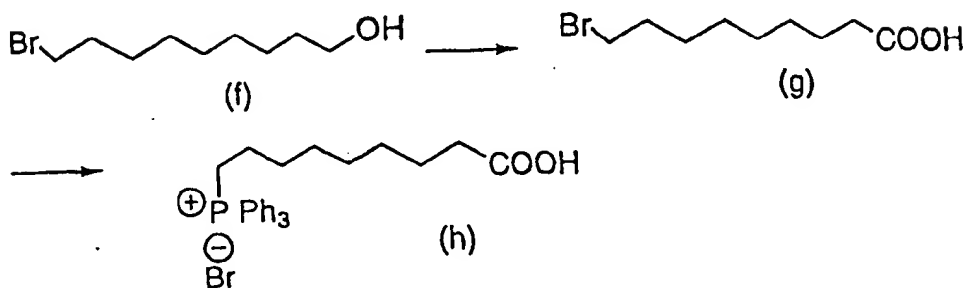
[0284] The preparation of 2-decarboxy-2-(4-carboxybutyl)-13,14-dihydro-15-keto-20-ethyl-PGF_{2α} isopropyl ester [IUPAC name: isopropyl Z-11-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-9-undecenoate] (28-4)



(28-4)

Preparation of the raw material compounds (8-carboxyoctyl)triphenylphosphonium bromide(h)

[0285]



[0286] 9-Bromononyl alcohol (f)(3.347g) was reacted with sodium metaperiodate and ruthenium chloride in the mixture of carbon tetrachloride, acetonitrile and water to give 9-bromononanoic acid(g).

[0287] Yield:2.632g(74.0%)

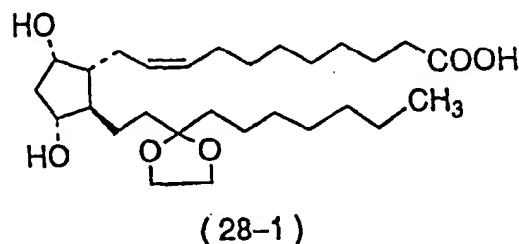
[0288] 9-Bromononanoic acid(g)(2.6103g) was reacted with triphenylphosphine in acetonitrile and (8-carboxyoctyl)triphenylphosphonium bromide(h) was obtained.

[0289] Yield:4.936g(89.9%)

Preparation of objective compound

28-1)

[0290] Z-11-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3,3-ethylenedioxydecyl)cyclopentyl]-9-undecenoic acid] (28-1)



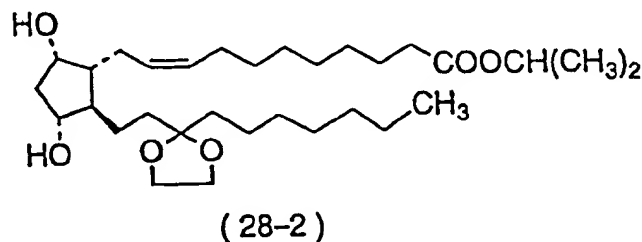
[0291] [1S,3(RS),5R,6R,7R]-6-(3,3-ethylenedioxydecyl-7-tetrahydropyranyloxy-2-oxabicyclo[3.3.0]octane-3-ol (1-a)(0.5600g) of Synthesis Example 1 was reacted with ylide prepared from (8-carboxyoctyl)triphenylphosphonium bromide(h) to give the compound (28-1) in the same way as 1-1) of Synthesis Example 1.

[0292] Yield:2.914g

28-2)

Isopropyl Z-11-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3,3-ethylenedioxydecyl) cyclopentyl]-9-undecenoate(28-2)

[0293]



[0294] The compound (28-1)(2.914g) was reacted with isopropyl iodide and DBU in acetonitrile and the resultant was subjected to silica gel column purification to give the compound (28-2).

[0295] Yield:0.4834g(57.6%)

28-3)

Isopropyl Z-11-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-9-undecenoate

[0296] The compound (28-2)(0.4834g) was dissolved in the mixture of acetic acid-THF-water and hold for two hours at 50°C. The resultant was purified on silica gel column to give the titled compound (28-4).

[0297] Yield:0.3593g(81.1%)

[0298] N.M.R.(CDCl₃) δ:0.88(3H,t,J=7.5Hz), 1.23(6H,d,J=6.5Hz), 1.25-1.95(26H,m), 1.95-2.19(3H,m), 2.27(2H,t,J=7.5Hz), 2.19-2.35(2H,m), 2.41(2H,t,J=7.5Hz), 2.572.57(2H,dt,J=7.5Hz,J=1.5Hz), 2.67(1H,d,J=7.5Hz), 3.89(1H,m), 4.19(1H,m), 5.00(1H,Sept,J=6.5 Hz), 5.42(2H,m).

Test Example 1

[0299] Japanese white male rabbit (2.5 to 2.8 kg body weight) was used, and 10⁻⁶ μl of endothelin-1 (ET-1: Peptide Kenkyusho) was administered into the corpus vitreum of the rabbit under urethane anesthesia, whereby circulation disorder of the optic disk was induced.

[0300] To the rabbit was once administered 35 μl of a physiological saline containing 0.006% of the test substance by means of ophthalmic administration 15 minutes before administration of the ET-1. To the control group was administered the same amount of physiological saline only.

[0301] Time-varying blood flow of the optic disk was measured by the use of a hydrogen clearance type tissue blood flowmeter (manufactured by Biomedical Science), and a relative blood flow of optic disk wherein the blood flow of optic disk prior to administration of ET-1 was considered to be 100% was determined.

[0302] Measurement of blood flow of optic disk was conducted as described hereinafter. An eyeball of a rabbit under urethane anesthesia was fixed at a slightly supravergent position, then, an acicular different electrode was inserted into the corpus vitreum from sclera on the side of more posterior pole of the eyeball than that of eyeball ring portion, and further inserted in the central portion of the optic disk (depth of insertion: 0.7 mm) under direct vision by employing a Vitrectomie lens. On one hand, an indifferent electrode was inserted under the skin of the head, and fixed thereto. The rabbit was allowed to inhale air containing 4% H₂ for 5 minutes under spontaneous respiration in accordance with open masking method, and blood flow of optic disk tissue (ml/minute/100 g tissue) was calculated from attenuation of hydrogen concentration in the tissue after stopping hydrogen inhalation by the use of hydrogen clearance type tissue blood flowmeter (manufactured by Biomedical Science).

[0303] The results are shown in Table 1 wherein elapsed time (minutes) was measured from the start 0 minute (at the time of administering ET-1).

Table 1

Test Substance	Number of Example (n)	Relative Blood Flow of Optic Disk (Average ± S.E.: %)				
		30	60	120	180	240 (min.)
Control	6	83.1 ± 5.0	75.9 ± 5.4	58.9 ± 8.1	55.3 ± 6.1	48.0 ± 2.4
Test Substance 1	3	109.0* ± 4.9	103.8* ± 1.6	89.3* ± 1.2	87.5* ± 5.1	79.5** ± 6.2

** P<0.01, * P<0.05 (Comparison with control group by Student's t-test)

Test Substance 1: 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-20-ethyl-PGF_{2α} isopropyl ester (the compound in synthesis example 1)

[0304] It can be seen from the above results that since the test substance 1 being the compound according to the present invention suppressed significantly circulation disorder of optic disk induced by endothelin, the substance had extremely strong endothelin antagonistic action.

Test Example 2

[0305] The same test as that of Test Example 1 was conducted except that the test substance 2 described hereunder was used as the substance to be tested.

[0306] The results are shown in Table 2.

Table 2

Test Substance	Number of Example (n)	Relative Blood Flow of Optic Disk (Average \pm S.E.: %)		
		60	150	240 (mm.)
Control	6	75.9 \pm 5.4	57.6 \pm 4.3	48.0 \pm 2.4
Test Substance 2	3	96.2 \pm 5.6	75.2 \pm 6.9	72.9** \pm 9.4

** P<0.01 (Comparison with control group by Student's t-test)

Test Substance 2: 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGE₁ isopropyl ester (compound in synthesis example 9)

Test Example 3

[0307] The same test as that of Test Example 1 was conducted except that the test substance 3 described hereunder was used as the substance to be tested.

[0308] The results are shown in Table 3.

Table 3

Test Substance	Number of Example (n)	Relative Blood Flow of Optic Disk (Average \pm S.E.: %)	
		210	240 (min.)
Control	6	54.3 \pm 6.5	48.0 \pm 2.4
Test Substance 3	3	80.6 \pm 8.1	74.6 \pm 6.0

Test Substance 3: 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGF₁ isopropyl ester (compound in synthesis example 23)

Test Example 4

[0309] The same test as that of Test Example 1 was conducted except that the test substance 4 described hereunder was used as the substance to be tested.

[0310] The results are shown in Table 4.

Table 4

Test Substance	Number of Example (n)	Relative Blood Flow of Optic Disk (Average \pm S.E.: %)				
		30	60 60	120 120	180	240 (min.)
Control	8	81.8 \pm 4.0	75.3 \pm 3.8	60.5 \pm 6.3	55.3 \pm 4.9	49.3 \pm 2.8
Test Substance 4	4	114.9** \pm 3.0	92.2 \pm 8.7	75.7 \pm 5.8	62.7* \pm 8.0	66.5* \pm 6.8

** P<0.01, * P<0.05 (Comparison with control group by Student's t-test)

Test Substance 4: 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluoro-20-ethyl-PGF_{2a} isopropyl ester (compound in synthesis example 17)

Test Example 5

[0311] The same test as that of Test Example 1 was conducted except that the test substance 5 described hereunder was used as the substance to be tested.

[0312] The results are shown in Table 5.

Table 5

Test Substance	Number of Example (n)	Relative Blood Flow Optic Disk (Average \pm S.E.: %)				
		30	60	120	180	240 (min.)
Control	8	81.8 \pm 4.6	75.3 \pm 3.8	60.5 \pm 6.3	55.3 \pm 4.9	49.3 \pm 2.8
Test Substance 5	4	96.7 \pm 4.2	93.8* \pm 4.4	80.8 \pm 2.9	86.5** \pm 2.9	80.2** \pm 5.3

** P<0.01, * P<0.05 (Comparison with control group by Student's t-test)

Test Substance 5: 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-dehydroxy-20-ethyl-PGF_{2a} isopropyl ester (compound in synthesis example 27)

Test Example 6

[0313] The same test as that of Test Example 1 was conducted except that the test substance 6 described hereunder was used as the substance to be tested.

[0314] The results are shown in Table 6.

Table 6

Test Substance	Number of Example (n)	Relative Blood Flow of Optic Disk (Average \pm S.E.: %)				
		30	60	120	180	240 (min.)
Control		81.8 \pm 4.6	75.3 \pm 3.8	60.5 \pm 6.3	55.3 \pm 4.9	49.3 \pm 2.8
Test Substance 6		96.6 \pm 7.1	96.9* \pm 8.9	89.9* \pm 7.3	83.0** \pm 4.3	74.8** \pm 5.5

** P<0.01, * P<0.05 (Comparison with control group by Student's t-test)

Test Substance 6: 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-PGF_{2a} isopropyl ester (compound in synthesis example 14)

Test Example 7

[0315] The same test as that of Test Example 1 was conducted except that the test substance 7 described hereunder was used as the substance to be tested.

[0316] The results are shown in Table 7.

Table 7

Test Substance	Number of Example (n)	Relative Blood Flow of Optic Disk (Average \pm S.E.: %)	
		90	180 (min.)
Control	8	66.0 \pm 5.0	55.3 \pm 4.9
Test Substance 7	4	75.4 \pm 7.0	61.0 \pm 5.6

Test Substance 7: 2-decarboxy-2-(4-carboxybutyl)-13,14-dihydro-15-keto-20-ethyl-PGF_{2a} isopropyl ester (compound in synthesis example 28)

Applicability in the Industry

[0317] The endothelin antagonist according to the present invention has extremely strong endothelin antagonistic action, and accordingly, it is effective for treating a variety of diseases and pathologies participated of endothelin. The term "treatment" described herein includes any means of control of the condition such as prevention, cure, relief of the condition, reduction of the condition, arrestation of development of the conditions.

[0318] Thus, the endothelin antagonist according to the present invention is useful for treating a variety of diseases and pathologies participated of endothelin, for example, hypertension, pulmonary hypertension, Buerger disease, primary Raynaud syndrome, asthma, eyegrounds (amphiblestroses, chorioidea, and the like) diseases, diabetes, arterial sclerosis, renal failure, cardiac infarction, angina pectoris, cerebrovascular contraction, and cerebral infarction, furthermore, multiple organ failures, and diseases such as disseminated intravascular coagulation due to endotoxin shock and the like, besides renal lesion induced by cyclosporin and the like as well as for treatment before and after organ transplantation such as liver transplant.

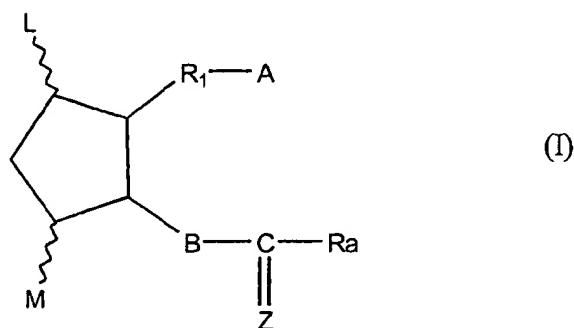
[0319] Since the endothelin antagonist according to the present invention has extremely strong endothelin antagonistic action as compared with that of a heretofore known prostanoid acid compound having 7 skeletal carbon atoms in α -chain, it is useful for treating a variety of diseases and pathologies participated of endothelin.

[0320] Accordingly, the endothelin antagonist according to the present invention is useful for treating a variety of diseases and pathologies participated of endothelin, for example, hypertension, pulmonary hypertension, Buerger disease, primary Raynaud syndrome, asthma, eyegrounds (amphiblestroses, chorioidea, and the like) diseases, diabetes, multiple organ failures, and diseases such as disseminated intravascular coagulation due to endotoxin shock and the like, besides renal lesion induced by cyclosporin and the like as well as for treatment before and after organ transplantation such as liver transplant. Particularly, the endothelin antagonist according to the present invention is effective for treating diseases and pathologies of eyegrounds (amphiblestroses, chorioidea, and the like) due to angiopathy participated of endothelin, for example, diabetic retinopathy, renal retinopathy, retinal venous occlusion and the like.

[0321] Besides, the compounds used for the present invention are extremely useful in view of separation of side effects such as cathartic, oxytocic action, as compared with that of a heretofore known prostanoid acid compound having 7 skeletal carbon atoms in α -chain.

Claims

1. Use of a prostanoid acid compound represented by the general formula (I):



wherein L and M are hydrogen, hydroxy, halogen, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, or oxo wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is -CH₂OH, -COCH₂OH, -COOH or its functional derivatives;

B is -CH₂-CH₂-, -CH=CH-, -C≡C-, -CH₂-CH₂-CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -C≡C-CH₂-, or -CH₂-C≡C-;

Z is

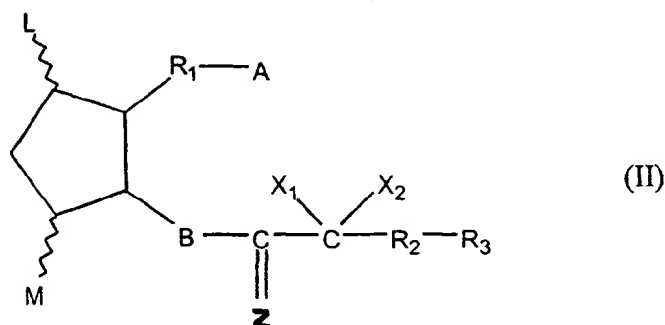


wherein R₄ and R₅ are hydrogen, hydroxy, C₁₋₆ alkyl, or C₁₋₆ alkoxy wherein R₄ and R₅ are not hydroxy and C₁₋₆ alkoxy at the same time;

R_1 is a divalent saturated or unsaturated aliphatic hydrocarbon residue having 7 to 12 carbon atoms, which is unsubstituted or substituted by halogen, oxo, or aryl; and

R_a is a saturated or unsaturated C_{1-14} aliphatic hydrocarbon residue which is unsubstituted or substituted by halogen, oxo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkanoyloxy, cyclo(C_{1-6})alkyl, aryl, or aryloxy for producing a pharmaceutical composition for the treatment of a disease caused by excess of endothelin.

2. The use as claimed in claim 1, wherein the skeletal carbon atoms in α -chain of said prostanoid acid compound are 9.
3. The use as claimed in claim 1, wherein said prostanoid acid compound is 2-decarboxy-2-(carboxy C_{1-6} alkyl)-prostaglandin compound.
4. The use as claimed in claim 1, wherein said prostanoid acid compound is 2-decarboxy-2-(carboxyethyl)-prostaglandin compound.
5. The use as claimed in claim 1, wherein said prostanoid acid compound is the one represented by the general formula (II):

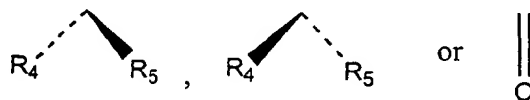


wherein L and M are hydrogen, hydroxy, halogen, C_{1-6} alkyl, hydroxy (C_{1-6})alkyl, or oxo wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_2OH$, $-COCH_2OH$, $-COOH$ or its functional derivatives;

B is $-CH_2-CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-CH_2-CH_2-CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C\equiv C-CH_2-$, or $-CH_2-C\equiv C-$;

Z is



wherein R_4 and R_5 are hydrogen, hydroxy, C_{1-6} alkyl, or C_{1-6} alkoxy wherein R_4 and R_5 are not hydroxy and C_{1-6} alkoxy at the same time;

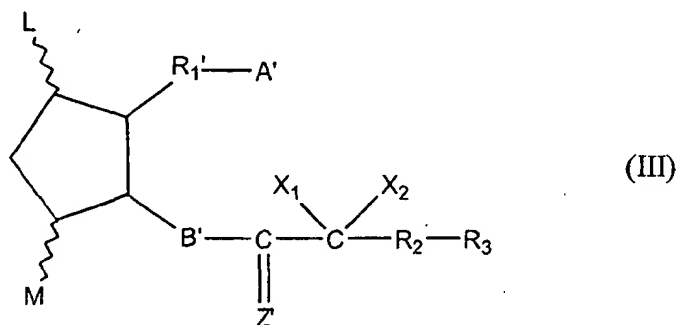
X_1 and X_2 are independently hydrogen, C_{1-6} alkyl, or halogen;

R_1 is a divalent saturated or unsaturated aliphatic hydrocarbon residue having 7 to 12 carbon atoms, which is unsubstituted or substituted by halogen, oxo, or aryl;

R_2 is a single bond or C_{1-6} alkylene; and

R_3 is C_{1-6} alkyl, C_{1-6} alkoxy, cyclo(C_{1-6})alkyl, aryl, or aryloxy.

6. The use of claim 1, in which the prostanoic acid compound is 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-ke-
to-20-ethyl-PGF₂α.
7. The use of claim 1, in which the prostanoic acid compound is 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-ke-
to-16,16-difluoro-20-ethyl-PGE₁.
8. The use of claim 1, in which the prostanoic acid compound is 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-ke-
to-16,16-difluoro-20-ethyl-PGF₁.
9. The use of claim 1, in which the prostanoic acid compound is 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-ke-
to-16,16-difluoro-20-ethyl-PGF₂α.
10. The use of claim 1, in which the prostanoic acid compound is 2-decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-ke-
to-PGF₂α.
11. A compound represented by the general formula (III):

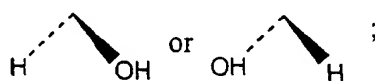


wherein L and M are hydrogen, hydroxy, halogen, C₁₋₆ alkyl, hydroxy(C₁₋₆)alkyl, or oxo wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A' is -COOH, or its functional derivatives;

B' is -CH₂-CH₂-;

Z' is



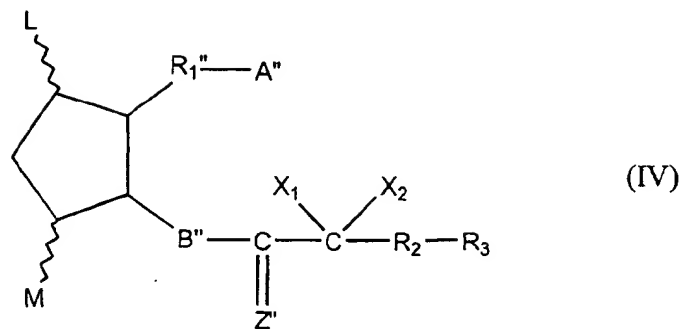
X₁ and X₂ are hydrogen, C₁₋₆ alkyl, or halogen wherein at least one of X₁ and X₂ is a halogen;

R₁' is a divalent saturated or unsaturated aliphatic hydrocarbon residue having 8 carbon atoms, which is unsubstituted or substituted by halogen, oxo, or aryl;

R₂ is a single bond or C₁₋₆ alkylene; and

R₃ is C₁₋₆ alkyl, C₁₋₆ alkoxy, cyclo (C₁₋₆)alkyl, aryl, or aryloxy.

12. A compound represented by the general formula (IV):



15 wherein L and M are hydrogen, hydroxy, halogen, C₁₋₆ alkyl, hydroxy (C₁₋₆)alkyl, or oxo wherein M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

20 A'' is -COOH, or its functional derivatives;

25 B'' is -CH₂-CH₂-, or -CH=CH-;

Z'' is



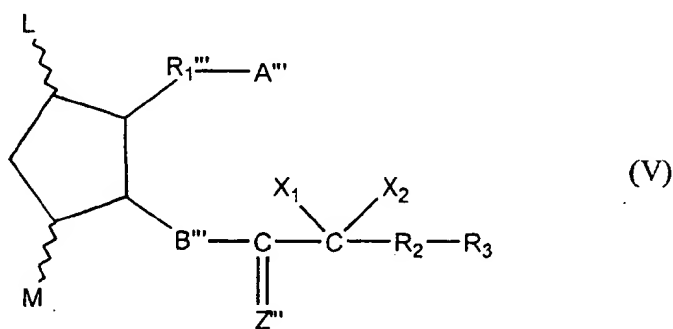
35 X₁ and X₂ are independently hydrogen, C₁₋₆ alkyl, or halogen;

40 R₁'' is a divalent saturated or unsaturated aliphatic hydrocarbon residue having 8 carbon atoms, which is unsubstituted or substituted by halogen, oxo, or aryl;

R₂ is a single bond or C₁₋₆ alkylene; and

45 R₃ is C₁₋₆ alkyl, C₁₋₆ alkoxy, cyclo(C₁₋₆)alkyl, aryl or aryloxy.

13. A compound represented by the general formula (V):



55 wherein L and M are hydrogen, hydroxy, halogen, C₁₋₆ alkyl, hydroxy (C₁₋₆)alkyl, or oxo wherein M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A''' is -COOH, or its functional derivatives;

B''' is -CH₂-CH₂-, or -CH=CH-;

Z''' is

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X₁ and X₂ are independently hydrogen, C₁₋₆ alkyl, or halogen;

R₁''' is a divalent saturated or unsaturated aliphatic hydrocarbon residue having 10 carbon atoms, which is unsubstituted or substituted by halogen, oxo, or aryl;

R₂ is a single bond or C₁₋₆ alkylene; and

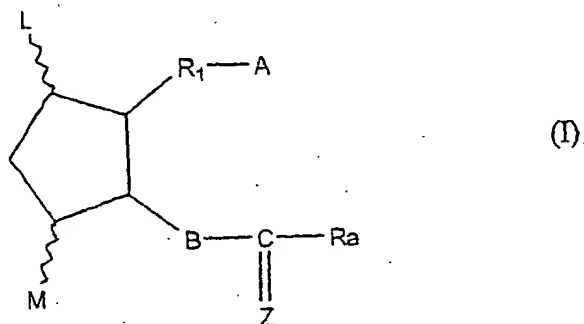
R₃ is C₁₋₆ alkyl, C₁₋₆ alkoxy, cyclo (C₁₋₆)alkyl, aryl, or aryloxy.

14. The compound as claimed in claim 12 in which the compound is 2-decarboxy-2-(2 carboxyethyl)-13,14-dihydro-15-dehydroxy-20-ethyl-PGF₂α.

15. The compound as claimed in claim 13, in which the compound is 2-decarboxy-2-(4-carboxybutyl)-13,14-dihydro-15-keto-20-ethyl-PGF₂α.

Patentansprüche

1. Verwendung einer Prostaglandin-Verbindung der allgemeinen Formel (I):



worin L und M für Wasserstoff, Hydroxy, Halogen, C₁₋₆-Alkyl, Hydroxy-(C₁₋₆)alkyl oder Oxo stehen, wobei mindestens eines von L und M eine andere Gruppierung als Wasserstoff ist und der fünfgliedrige Ring mindestens eine Doppelbindung haben kann;

A für -CH₂OH, -COCH₂OH, -COOH oder funktionelle Derivate davon steht;

B für -CH₂-CH₂-, CH=CH-, -C≡C-, -CH₂-CH₂-CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -C≡C-CH₂- oder -CH₂-C≡C steht;

Z für



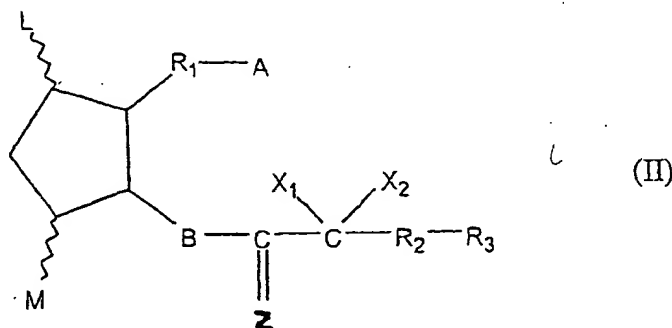
steht,

worin R_4 und R_5 für Wasserstoff, Hydroxy, C_{1-6} -Alkyl oder C_{1-6} -Alkoxy stehen, wobei R_4 und R_5 nicht Hydroxy und C_{1-6} -Alkoxy zur gleichen Zeit sind;

R_1 für einen zweiwertigen gesättigten oder ungesättigten aliphatischen Kohlenwasserstoffrest mit 7 bis 12 Kohlenstoffatomen steht, der unsubstituiert ist oder durch Halogen, Oxo oder Aryl substituiert ist; und

R_a für einen gesättigten oder ungesättigten aliphatischen C_{1-14} -Kohlenwasserstoffrest steht, der unsubstituiert ist oder durch Halogen, Oxo, Hydroxy, C_{1-6} -Alkoxy, C_{1-6} -Alkanoyloxy, Cyclo- (C_{1-6}) alkyl, Aryl oder Aryloxy substituiert ist, zur Herstellung eines Medikaments zur Behandlung von Erkrankungen, die durch einen Überschuss an Endothelin hervorgerufen werden.

2. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Anzahl der Skelett-Kohlenstoffatome in der α -Kette der Prostansäureverbindung 9 ist.
3. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Prostansäureverbindung die 2-Decarboxy-2-(carboxy- C_{1-6} -alkyl)prostaglandinverbindung ist.
4. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Prostansäureverbindung die 2-Decarboxy-2-(carboxyethyl)prostaglandinverbindung ist.
5. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Prostansäureverbindung eine solche ist, die durch die allgemeine Formel (II)

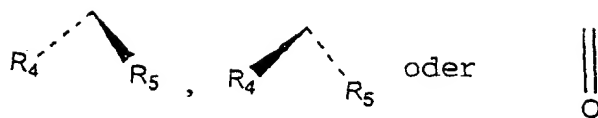


angegeben wird, worin L und M für Wasserstoff, Hydroxy, Halogen, C_{1-6} -Alkyl, Hydroxy- (C_{1-6}) alkyl oder Oxo stehen, worin mindestens eines von L und M eine andere Gruppe als Wasserstoff ist und der fünfgliedrige Ring mindestens eine Doppelbindung besitzen kann;

A für $-CH_2OH$, $-COCH_2OH$, $-COOH$ oder funktionelle Derivate davon steht;

B für $-CH_2-CH_2-$, $CH=CH$, $-C\equiv C-$, $-CH_2-CH_2-CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C\equiv C-CH_2-$ oder $-CH_2-C\equiv C$ steht;

Z für



steht,

worin R_4 und R_5 für Wasserstoff, Hydroxy, C_{1-6} -Alkyl oder C_{1-6} -Alkoxy stehen, wobei R_4 und R_5 nicht Hydroxy und C_{1-6} -Alkoxy zur gleichen Zeit sind;

X_1 und X_2 unabhängig voneinander für Wasserstoff, C_{1-6} -Alkyl oder Halogen stehen;

R_1 für einen zweiwertigen ungesättigten aliphatischen Kohlenwasserstoffrest mit 7 bis 12 Kohlenstoffatomen steht, der unsubstituiert ist oder durch Halogen, Oxo oder Aryl substituiert ist;

R_2 für eine Einfachbindung oder C_{1-6} -Alkylen steht; und

R_3 für C_{1-6} -Alkyl, C_{1-6} -Alkoxy, Cyclo- (C_{1-6}) alkyl, Aryl oder Aryloxy steht.

6. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Prostansäureverbindung 2-Decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-20-ethyl-PGF₂ α ist.

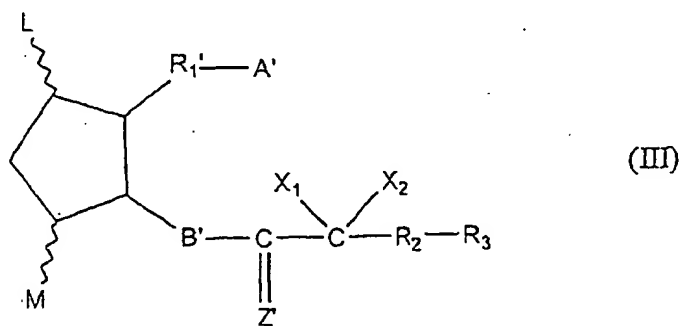
7. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Prostansäureverbindung 2-Decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluor-20-ethyl-PGE₁ ist.

8. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Prostansäureverbindung 2-Decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluor-20-ethyl-PGF₁ ist.

9. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Prostansäureverbindung 2-Decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-16,16-difluor-20-ethyl-PGF₂ α ist.

10. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, dass** die Prostansäureverbindung 2-Decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-keto-PGF₂ α ist.

11. Verbindung der allgemeinen Formel (III):

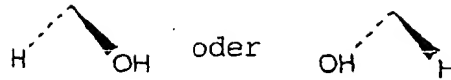


worin L und M für Wasserstoff, Hydroxy, Halogen, C_{1-6} -Alkyl, Hydroxy- (C_{1-6}) alkyl oder Oxo stehen, wobei mindestens eines von L und M eine andere Gruppierung als Wasserstoff ist und der fünfgliedrige Ring mindestens eine Doppelbindung haben kann;

A' für $-COOH$ oder funktionelle Derivate davon steht;

B' für $-CH_2-CH_2-$ steht;

Z' für



steht;

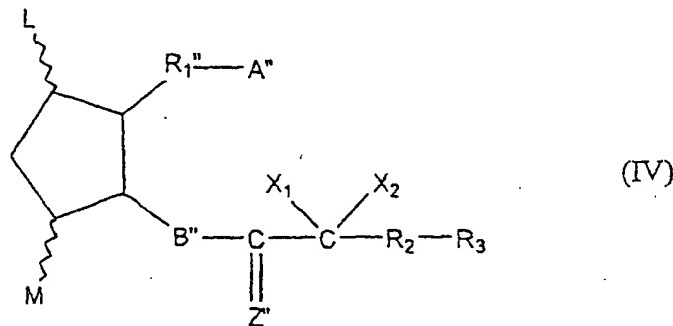
X_1 und X_2 für Wasserstoff, C_{1-6} -Alkyl oder Halogen stehen, wobei mindestens eines von X_1 und X_2 ein Halogen ist;

R_1' für einen zweiwertigen gesättigten oder ungesättigten aliphatischen Kohlenwasserstoffrest mit 8 Kohlenstoffatomen steht, der unsubstituiert ist oder durch Halogen, Oxo oder Aryl substituiert ist;

R_2 für eine Einfachbindung oder C_{1-6} -Alkylen steht; und

R_3 für C_{1-6} -Alkyl, C_{1-6} -Alkoxy, Cyclo- (C_{1-6}) alkyl, Aryl oder Aryloxy steht.

12. Verbindung der allgemeinen Formel (IV) :



worin L und M für Wasserstoff, Hydroxy, Halogen, C_{1-6} -Alkyl, Hydroxy- (C_{1-6}) alkyl oder Oxo stehen, wobei M eine andere Gruppierung als Wasserstoff ist und der fünfgliedrige Ring mindestens eine Doppelbindung haben kann;

A'' für $-COOH$ oder funktionelle Derivate davon steht;

B'' für $-CH_2CH_2-$ oder $-CH=CH$ steht;

Z'' für



steht;

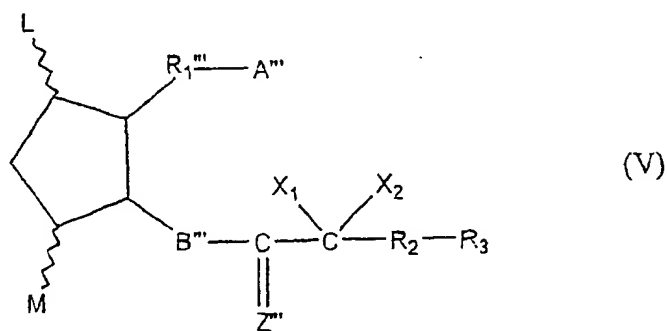
X_1 und X_2 unabhängig voneinander für Wasserstoff, C_{1-6} -Alkyl oder Halogen stehen;

R_1'' für einen zweiwertigen gesättigten oder ungesättigten aliphatischen Kohlenwasserstoffrest mit 8 Kohlenstoffatomen steht, der unsubstituiert ist oder durch Halogen, Oxo oder Aryl substituiert ist;

R_2 für eine Einfachbindung oder C_{1-6} -Alkylen steht; und

R_3 für C_{1-6} -Alkyl, C_{1-6} -Alkoxy, Cyclo-(C_{1-6})alkyl, Aryl oder Aryloxy steht.

13. Verbindung der allgemeinen Formel (V):



worin L und M für Wasserstoff, Hydroxy, Halogen, C_{1-6} -Alkyl, Hydroxy-(C_{1-6})alkyl oder Oxo stehen, wobei M eine andere Gruppierung als Wasserstoff ist und der fünfgliedrige Ring mindestens eine Doppelbindung haben kann;

A''' für $COOH$ oder funktionelle Derivate davon steht;

B''' für $-CH_2-CH_2-$ oder $-CH=CH-$ steht;

Z''' für



steht;

X_1 und X_2 unabhängig voneinander für Wasserstoff, C_{1-6} -Alkyl oder Halogen stehen;

R_1''' für einen zweiwertigen gesättigten oder ungesättigten aliphatischen Kohlenwasserstoffrest mit 10 Kohlenstoffatomen steht, der unsubstituiert oder durch Halogen, Oxo oder Aryl substituiert ist;

R_2 für eine Einfachbindung oder C_{1-6} -Alkylen steht; und

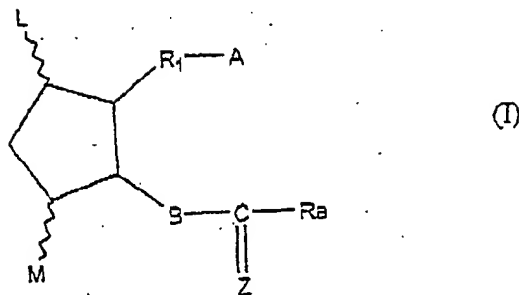
R_3 für C_{1-6} -Alkyl, C_{1-6} -Alkoxy, Cyclo-(C_{1-6})alkyl oder Aryloxy steht.

14. Verbindung nach Anspruch 12, **dadurch gekennzeichnet, dass** die Verbindung 2-Decarboxy-2-(2-carboxyethyl)-13,14-dihydro-15-dehydroxy-20-ethyl-PGF₂α ist.

15. Verbindung nach Anspruch 13, **dadurch gekennzeichnet, dass** die Verbindung 2-Decarboxy-2-(4-carboxybutyl)-13,14-dihydro-15-keto-20-ethyl-PGF₂α ist.

Revendications

1. Utilisation d'un composé acide prostanoïque représenté par la formule générale (I) ci-dessous:

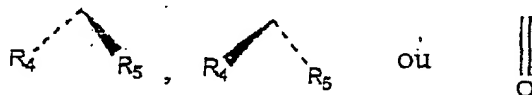


dans laquelle L et M désignent un atome d'hydrogène, un groupe hydroxy, halogène, alkyle en C₁₋₆, hydroxy (alkyle en C₁₋₆), ou oxo, au moins un des groupes L et M étant autre que l'hydrogène, et où le cycle à cinq chaînons peut posséder au moins une double liaison ;

A est -CH₂OH, -COCH₂OH, -COOH ou un de ses dérivés fonctionnels ;

B est -CH₂CH₂-, -CH=CH-, -C≡C-, -CH₂-CH₂-CH₂-, -CH=CH-CH₂-, CH₂-CH=CH-, -C≡C-CH₂-, ou -CH₂-C≡C-;

Z est

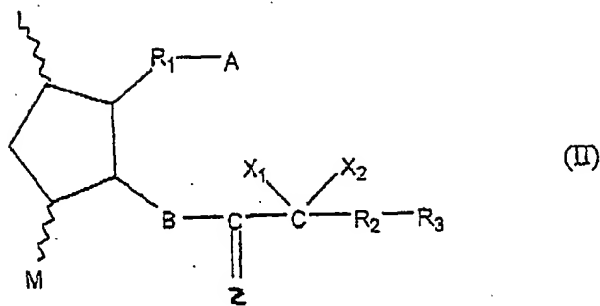


où R₄ et R₅ désignent un atome d'hydrogène, un groupe hydroxy, alkyle en C₁₋₆ ou alcoxy en C₁₋₆, R₄ et R₅ n'étant pas simultanément un groupement hydroxy et un groupement alcoxy en C₁₋₆ ;

R₁ est un radical hydrocarboné aliphatique divalent, saturé ou insaturé, possédant de 7 à 12 atomes de carbone, lequel est non substitué, ou substitué par un groupement halogène, oxo, ou aryle ; et

R_a est un radical hydrocarboné aliphatique, saturé ou insaturé, en C₁₋₁₄, lequel est non substitué ou substitué par un groupement halogène, oxo, hydroxy, alcoxy en C₁₋₆, alcanoyloxy en C₁₋₆, cyclo(alkyle en C₁₋₆), aryle, ou aryloxy, pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie causée par un excès d'endothéline.

2. Utilisation selon la revendication 1, où le nombre d'atomes de carbone dans le squelette de la chaîne en α dudit composé d'acide prostanoïque est de 9.
3. Utilisation selon la revendication 1, où ledit composé acide prostanoïque est un composé 2-décarboxy-2-[carboxy-(alkyle en C₁₋₆)]-prostaglandine.
4. Utilisation selon la revendication 1, où ledit composé acide prostanoïque est le composé 2-décarboxy-2-(carboxyéthyl)-prostaglandine.
5. Utilisation selon la revendication 1, où ledit composé acide prostanoïque est un composé représenté par la formule générale (II) ci-dessous:



dans laquelle L et M désignent un atome d'hydrogène, un groupe hydroxy, halogène, alkyle en C₁₋₆, hydroxy (alkyle en C₁₋₆), ou oxo, au moins un des groupes L et M étant autre que l'hydrogène, et où le cycle à cinq chaînons peut posséder au moins une double liaison ;

A est -CH₂OH, -COCH₂OH, -COOH ou un de ses dérivés fonctionnels ;

B est -CH₂CH₂-, -CH=CH-, -C≡C-, -CH₂-CH₂-CH₂-, -CH=CH-CH₂-, CH₂-CH=CH-, -C≡C-CH₂-, ou -CH₂-C≡C- ;

Z est



où R₄ et R₅ désignent un atome d'hydrogène, un groupe hydroxy, alkyle en C₁₋₆ ou alcoxy en C₁₋₆, R₄ et R₅ n'étant pas simultanément des groupements hydroxy ou alcoxy en C₁₋₆ ;

X₁ et X₂ désignent indépendamment l'un de l'autre, un atome d'hydrogène, un groupement alkyle en C₁₋₆, ou un halogène ;

R₁ est un radical hydrocarboné aliphatique divalent, saturé ou insaturé, possédant de 7 à 12 atomes de carbone, lequel est non substitué, ou substitué par un groupement halogène, oxo, ou aryle ;

R₂ est une simple liaison ou un groupement alkylène en C₁₋₆ ; et

R₃ est un groupement alkyle en C₁₋₆, alcoxy en C₁₋₆, cyclo(alkyle en C₁₋₆), aryle ou aryloxy.

6. Utilisation selon la revendication 1, dans laquelle le composé acide prostanoïque est le 2-décarboxy-2-(2-carboxyéthyl)-13,14-dihydro-15-céto-20-éthyl-PGF_{2α}.

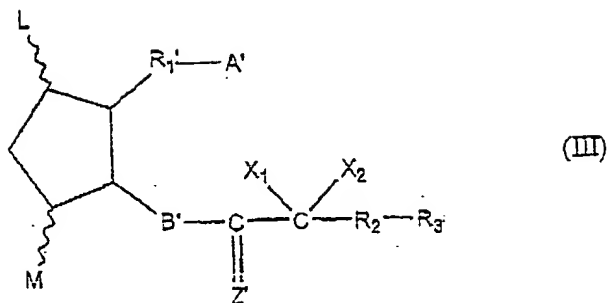
7. Utilisation selon la revendication 1, dans laquelle le composé acide prostanoïque est le 2-décarboxy-2-(2-carboxyéthyl)-13,14-dihydro-15-céto-16,16-difluoro-20-éthyl-PGE₁.

8. Utilisation selon la revendication 1, dans laquelle le composé acide prostanoïque est le 2-décarboxy-2-(2-carboxyéthyl)-13,14-dihydro-15-kéto-16,16-difluoro-20-éthyl-PGF₁.

9. Utilisation selon la revendication 1, dans laquelle le composé acide prostanoïque est le 2-décarboxy-2-(2-carboxyéthyl)-13,14-dihydro-15-céto-16,16-difluoro-20-éthyl-PGF_{2α}.

10. Utilisation selon la revendication 1, dans laquelle le composé acide prostanoïque est le 2-décarboxy-2-(2-carboxyéthyl)-13,14-dihydro-15-céto-PGF_{2α}.

11. Composé représenté par la formule générale (III) ci-dessous :

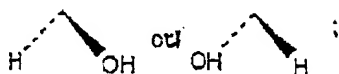


dans laquelle L et M désignent un atome d'hydrogène, un groupe hydroxy, halogène, alkyle en C₁₋₆, hydroxy (alkyle en C₁₋₆), ou oxo, au moins un des groupes L et M étant autre que l'hydrogène, et où le cycle à cinq chaînons peut posséder au moins une double liaison ;

A' est -COOH, ou un de ses dérivés fonctionnels ;

B' est -CH₂-CH₂- ;

Z' est



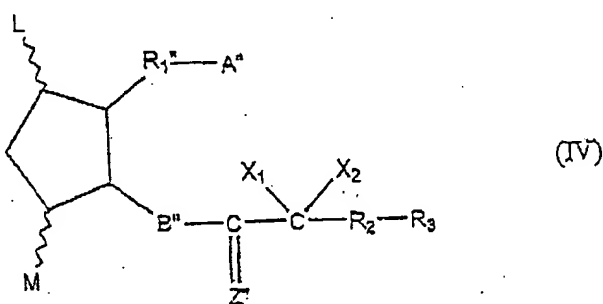
X₁ et X₂ désignent un atome d'hydrogène, un groupe alkyle en C₁₋₆, ou halogène, avec au moins un de X₁ et X₂ représentant un halogène ;

R₁' est un radical hydrocarboné aliphatique divalent, saturé ou insaturé, possédant 8 atomes de carbone, lequel est non substitué, ou substitué par un groupement halogène, oxo, ou aryle ;

R₂ est une simple liaison ou un groupe alkylène en C₁₋₆ ; et

R₃ est un groupement alkyle en C₁₋₆, alcoxy en C₁₋₆, cyclo(alkyle en C₁₋₆), aryle, ou aryloxy.

12. Composé représenté par la formule générale (IV) ci-dessous :



dans laquelle L et M désignent un atome d'hydrogène, un groupe hydroxy, halogène, alkyle en C₁₋₆, hydroxy (alkyle en C₁₋₆), ou oxo, au moins un des groupes L et M étant autre que l'hydrogène, et où le cycle à cinq chaînons peut posséder au moins une double liaison ;

A'' est -COOH, ou un de ses dérivés fonctionnels ;

B'' est -CH₂CH₂-, ou -CH=CH- ;

Z'' est



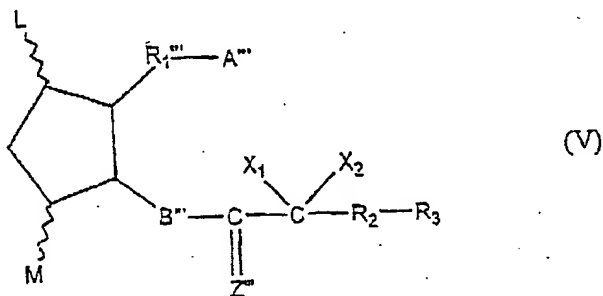
X_1 et X_2 désignent indépendamment l'un de l'autre un atome d'hydrogène, un groupement alkyle C_{1-6} , ou un halogène ;

R_1'' est un radical hydrocarboné aliphatique divalent, saturé ou insaturé, possédant 8 atomes de carbone, lequel est non substitué ou substitué par un groupement halogène, oxo, ou aryle ;

R_2 est une simple liaison ou un groupe alkylène en C_{1-6} ; et

R_3 est un groupement alkyle en C_{1-6} , alcoxy en C_{1-6} , cyclo(alkyle en C_{1-6}), aryle ou aryloxy.

13. Composé représenté par la formule générale (V) ci-dessous :



dans laquelle L et M désignent un atome d'hydrogène, un groupe hydroxy, halogène, alkyle en C_{1-6} , hydroxy (alkyle en C_{1-6}), ou oxo, au moins un des groupes L et M étant autre que l'hydrogène, et où le cycle à cinq chaînons peut posséder au moins une double liaison ;

A''' est $-COOH$, ou un de ses dérivés fonctionnels ;

B''' est $-CH_2CH_2-$, ou $-CH=CH-$;

Z''' est



X_1 et X_2 sont indépendamment l'un de l'autre, un atome d'hydrogène, un groupement alkyle en C_1-C_6 , ou un halogène ;

R_1''' est un radical hydrocarboné aliphatique divalent, saturé ou insaturé, possédant 8 atomes de carbone, lequel est non substitué, ou substitué par un groupement halogène, oxo, ou aryle ;

R_2 est une simple liaison ou un groupe alkylène en C_{1-6} ; et

R_3 est un groupement alkyle en C_{1-6} , alcoxy en C_{1-6} , cyclo(alkyle en C_{1-6}), aryle ou aryloxy.

14. Composé selon la revendication 12, ledit composé étant le 2-décarboxy-2-(2-carboxyéthyl)-13,14-dihydro-15-déhydroxy-20-éthyl-PGF $_2\alpha$.

15. Composé selon la revendication 13, ledit composé étant le 2-décarboxy-2-(4-carboxybutyl)-13,14-dihydro-15-céto-20-éthyl-PGF $_2\alpha$.